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CRANIOPHARYNGIOMA IN THE ELDERLY

BY

R. W. ROSS RUSSELL* and J. B. PENNYBACKER

From the Departments of Neurology and Neurological Surgery, Radcliffe Infirmary, Oxford

Although craniopharyngiomas comprise only a small proportion of intracranial tumours, by virtue of a unique situation close to what Cushing called the mainspring of primitive existence, they have an interest and importance out of proportion to their numbers. Since the tumours are congenital it is not surprising that the majority should present early in life, and many descriptions have been given to the effects produced in children and young adults. It used to be thought that the finding of a craniopharyngioma in an older patient was a rarity, but it now appears that an appreciable proportion of patients have their first symptoms after the age of 40, and that important differences exist between these and younger patients. In children there are two main syndromes: first, visual failure from compression of the optic nerve and chiasm, and secondly, symptoms and signs of increased intracranial pressure such as headache, papilloedema, and separation of the cranial sutures without specific visual field defects. This latter group results from obstruction of the third ventricle by the tumour. Evidence of hypothalamic and pituitary damage, as shown by various forms of endocrine or growth abnormality, is common, and radiological calcification is often seen. In adults there is much less tendency for the tumour to obstruct the flow of cerebrospinal fluid and the incidence of endocrine abnormality also falls sharply. Visual failure from chiasmal compression remains common, and mental disturbance, a rare feature in young patients, becomes of increasing importance. It is with these two features that this report is chiefly concerned.

Clinical Material

Between the years 1938 and 1959 in the records of the Departments of Neurological Surgery and Neurology at the Radcliffe Infirmary, Oxford, there were 46 patients in whom a diagnosis of craniopharyngioma was proved at operation or necropsy. There were a further 22 in whom the diagnosis was made on the combination of radiological and clinical findings. Of this total of 68 patients, 24 were middle aged or elderly. There were six in the fifth decade, nine in the sixth decade, eight in the seventh decade, and one in the eighth, the average age of these patients being 57·4 years. There were 11 women and 13 men. The diagnosis was confirmed by operation or necropsy in 18, and in the remaining six was made on the clinical and radiological findings.

Fourteen patients came under observation because of visual failure with or without headaches, eight because of mental disturbance, one because of seizures, and one because of a radiograph for an unrelated condition.

The majority of patients had symptoms for months or years before seeking advice and in three patients there was a history of recent head injury.

Details of the visual symptoms and signs are set out below.

Visual Failure.—Visual failure was the commonest symptom in this group of patients, and of 24 patients only one had normal visual acuity with full fields. It was not uncommon, however, for visual failure to occur without the patient's knowledge either because central vision was retained at least in one eye, or because of advanced mental symptoms. Four patients with dementia who denied visual symptoms were found to have abnormal acuity or fields.

The duration of visual symptoms before the patient sought advice was very variable, but in the majority (12 patients) it was between six months and two years. Six patients had symptoms for two to five years before seeking advice and one for over 10 years. To the majority of patients visual failure had seemed slowly progressive but marked fluctuation in the visual state both subjectively and objectively was a notable feature in seven cases. In one of these (Case 2) acuity was measured under identical conditions over the space of six months and the acuity at two-monthly intervals was on the right side J.8, J.8 and no perception of light; on the left side J.10, J.2, J.16.

*E. G. Fearnsides scholar, University of Cambridge.

TABLE I
SURGICAL TREATMENT AND FOLLOW-UP

Case No.	Treatment	Outcome	Duration of Illness since First Seen
1	Partial removal	Dead	Post-operative
2	Aspiration, biopsy	Dead, vision improved post-operatively	15 months
3	Partial removal	Alive, no symptoms, mentally alert	1 year
4	Partial removal	Alive, active, mentally normal	5 years
5	Removal	Dead	3 months
6	None	Dead	1 year
7	None	Alive, vision unchanged, mentally normal	3 years
8	None	Alive, occasional seizures, no visual change	3 years
9	Partial removal	No information available	
10	Partial removal and aspiration	Dead	1 year
11	Aspiration, ventriculocisternostomy	Dead	1 year
12	Biopsy	Alive, slow visual deterioration	7 years
13	Removal	Alive 3 months later	No further information
14	None	Alive, unchanged, mentally alert	10 years
15	Partial removal	Dead	Post-operative
16	Aspiration, ventriculocisternostomy	Dead	3 months
17	Partial removal	Dead	Post-operative
18	Removal	Alive, memory very poor, vision improved post-operatively	18 years
19	Partial removal	Alive, hypopituitary state	20 years
20	Partial removal	Dead, vision improved post-operatively	4 years
21	None	Alive, organic dementia	15 years
22	None	Alive, aged but alert	20 years
23	None	Alive, unchanged	3 months
24	Aspiration, ventriculocisternostomy	Dead	4 months

The field changes were not uniform and the different types of defect are listed in Table I, which includes all patients on whom reliable quantitative perimetry was done. In the great majority of patients the defect was bitemporal though a considerable difference between the fields in the two eyes was not uncommon. In cases seen early, the bitemporal field defect could be of the depressional or scotomatous variety, the scotomata often being paracentral and terminating sharply at the vertical meridian. The defect began in the upper or lower temporal quadrants with equal frequency. In the scotomatous type peripheral isopters usually showed some temporal depression in addition to the central loss.

One patient had an incomplete bitemporal hemianopia with a central scotoma in one eye and in another case the scotoma was in the lower nasal field. Two patients showed a homonymous defect, in one combined with a paracentral scotoma. The various types of field loss are illustrated in Figs. 1-8.

Changes in the optic discs were less frequent and less reliable than those in acuity or fields. Thus 10 patients had normal fundi with well-marked field changes and a further five showed some pallor of one or both discs, of doubtful significance. In nine cases there was unequivocal optic atrophy and in one bilateral papilloedema.

One patient (Case 8) experienced visual hallucinations of an unformed type occurring two or three times a day. In these he had a similar and arresting impression of vague objects moving on the right side, although it is not clear whether the hallucinations occurred in homonymous fields or were confined to the right eye. He also suffered from sudden falling attacks without warning and these were independent of the visual symptoms. Field charting showed a bitemporal hemianopia of depressional type.

Following partial removal or aspiration of the tumour four patients showed objective evidence of considerable visual improvement, one showed slight improvement, and eight were unchanged or deteriorated. Improvement showed no definite correlation with the preexisting optic atrophy but of the five patients who improved four had normal or near-normal discs, while of the six who showed no improvement three had normal fundi at the time of operation.

Six patients had no operation and of these one deteriorated rapidly to complete blindness while five showed no change or slow deterioration over years.

Mental Aspects.—In all patients observations were made regarding level of consciousness, orientation, mood, memory, and simple tests of learning and calculation. In 12 patients no defect could be found but the other 12 patients showed various degrees of abnormality (Table I). In four this amounted to a slight or moderate deterioration in recent memory with a tendency to somnolence, apathy, and loss of interest. In eight, however, the mental disturbance was more profound and dominated the clinical picture leading in three cases to admission to mental hospitals. Two of these eight patients have been reported in full (Williams and Pennybacker, 1954) and the remaining case histories are given below.

Case Reports

Case 4 (U.O.H. 133629).—V.S., an active housewife of 52, experienced a gradual visual blurring affecting the outer halves of her field of vision, first noticed when

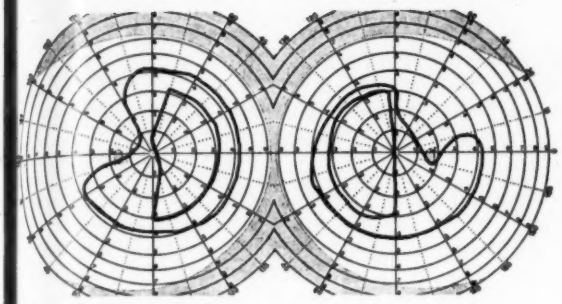

FIG. 1.—Case 2: Bitemporal hemianopia, depressional type.
Visual fields to 30/2,000 2/2,000, white.

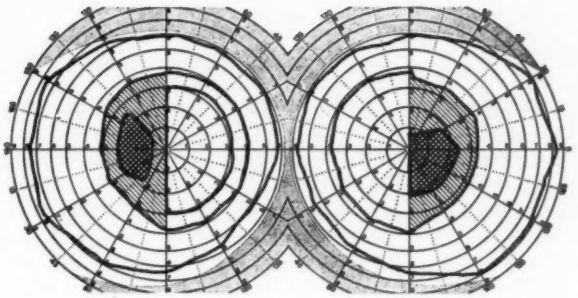

FIG. 2.—Case 18: Bitemporal hemianopia, scotomatous type.
Visual fields to 5/330, 20/2,000, 10/2,000 white.
Scotomata to 20/2,000 (absolute and relative).

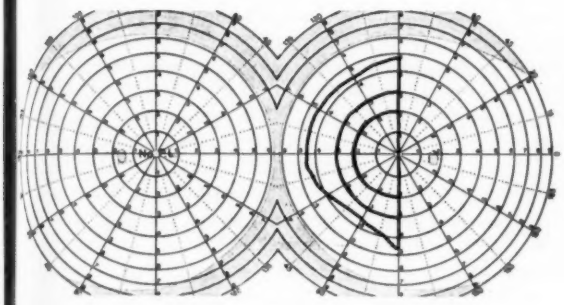

FIG. 3.—Case 19: Right temporal hemianopia and blind left eye.
Visual fields to 10/330, 50/2,000, 5/2,000 white.

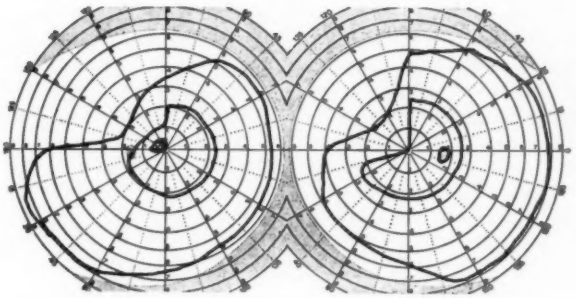

FIG. 4.—Case 6: Homonymous hemianopia with paracentral scotoma.
Visual fields to 5/330, 1/2,000 white.
Scotoma to 10/2,000.

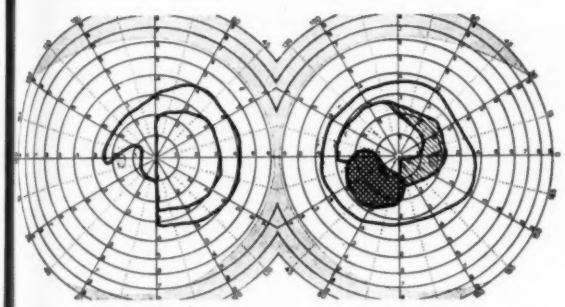

FIG. 5.—Case 13: Incomplete bitemporal hemianopia with large nasal scotoma.
Visual fields to 200/2,000, 50/2,000 white.
Scotomata to 200/2,000 (absolute and relative).

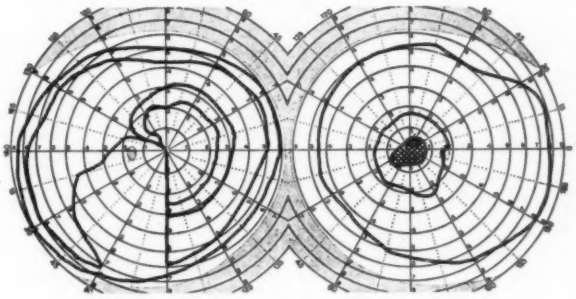

FIG. 6.—Case 24: Left incomplete temporal hemianopia with right central scotoma.
Visual fields (left eye) to 3/330, 1/330, 5/2,000, 2/2,000 white; (right eye) to 3/330, 10/2,000, 2/2,000.
Scotoma to 10/2,000.

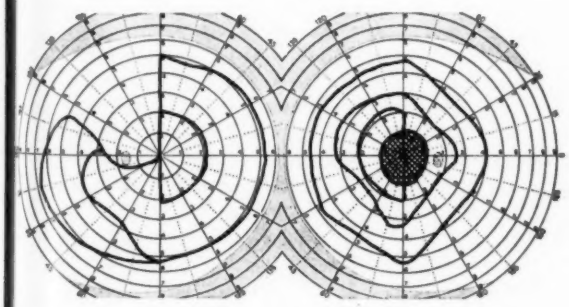

FIG. 7.—Case 3: Left incomplete temporal hemianopia with right central scotoma.
Visual fields to 10/330, 3/330, 5/2,000 white (left eye); 5/330, 40/2,000, 20/2,000 white (right eye).
Scotoma to 40/2,000.

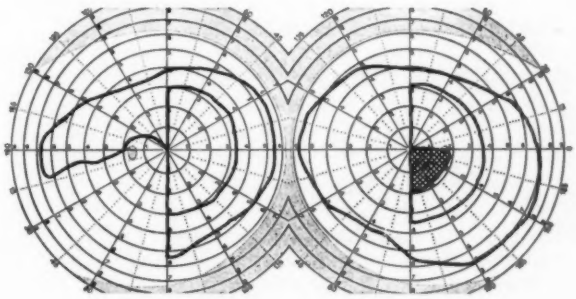

FIG. 8.—Case 17: Bitemporal hemianopia with unilateral scotoma.
Visual fields to 3/330, 2/2,000 white (left eye); 5/330, 20/2,000 white (right eye).
Scotoma to 20/2,000.

crossing the road. Central vision was spared and she was able to sew and read. After some months, during which her vision slowly deteriorated, she was noticed to be excessively tired and drowsy and to lose her appetite. She began talking constantly of events in the distant past and became confused about the date and the time of day. When her family asked how she had spent the day, she would invent impossible stories of visits to faraway friends. At times she appeared to believe she was 20 years old and talked of the events of 30 years ago as though they had just occurred. At first these mental symptoms alternated with periods of lucidity but later the confusion became constant. She occasionally complained of headaches and often of excessive cold in the winter; she was always thirsty, drinking 15 cups of tea a day.

Her past health had been excellent although the menses had been a little irregular and she had borne no children. The menopause occurred at the age of 50 and libido had been diminished since that time.

After two years of symptoms, she was admitted to the Radcliffe Infirmary under the care of Dr. E. M. Buzzard and by that time the mental changes were so pronounced that a history had to be obtained from relatives.

She tended to sleep most of the day but when roused would talk incessantly and in a friendly fashion to anyone who would listen. At times she was quite lucid, was able approximately to recall the date, and realized she was ill and in hospital. On another occasion only two hours later she was hopelessly confused, was 10 years behind with the date, and thought she was at home.

She was very distractable and could not attempt simple tests of mental arithmetic. Vocabulary was low average on the Wechsler scale and there was no dysphasia. Memory for remote personal events was fair but for recent events it was very poor. When asked to repeat a story she altered and distorted it after a few seconds. Learning was also severely affected and she was easily confused and fatigued.

Physical examination revealed a pale and rather obese woman with atrophic dry skin. The scalp hair was fine, dry, and brittle and the body hair of normal distribution apart from moderate facial growth. The breasts and genitalia were normal.

In the central nervous system there was no anosmia and visual acuity was restricted to hand movements in the upper nasal quadrants. The fundi showed bilateral optic atrophy and the pupils reacted sluggishly to light.

There were no other abnormalities.

Investigations.—The cerebrospinal fluid was under normal pressure, with 4 lymphocytes/c.mm. and protein 70 mg./100 ml. The Wassermann reaction was negative and the Lange curve 0-0.

A radiograph of the skull showed that the pituitary fossa was intact but a calcified area lay above and behind the clivus. An air encephalogram showed a large space-occupying lesion above the sella in the midline growing into the third ventricle and deforming the anterior horns of the lateral ventricle. Calcification appeared to be outside the mass. There was no hydrocephalus.

Haemoglobin was 100% and the B.M.R. 19%. The fasting blood sugar level was 79 mg./100 ml. The 17-ketosteroids (neutral) were 2 mg./24 hours.

Operation.—The tumour was approached by elevating the right frontal lobe; the optic nerves and anterior border of the chiasma appeared normal. It was seen at the posterior border of the chiasma and appeared to be arising from above rather than from the sella. The tumour was found to be partly cystic and 30 ml. of viscid yellow fluid was aspirated. No removal was attempted.

Progress.—Mental testing three days later showed a considerable improvement. The patient was correctly orientated, alert and cooperative, and was able to recall some of the tests she had attempted pre-operatively. Vocabulary learning tests were about the same.

Two days later, however, she began behaving strangely and threw cups and saucers at patients across the ward in the belief that they were poisoning her. She also suffered from visual hallucinations and poured jugs of water over imaginary assailants.

This state of paranoid confusion lasted about 10 days and she then began to improve again. Visual acuity two weeks after the operation was L 6/36, J. 12, R 6/60, J. 20. She was discharged after three weeks.

In the following months her mental state became quite normal and acuity reached VAL 6/9, J.4, VAR 6/60, J.19. Five months later, however, visual failure and headache returned, although she remained mentally clear. Acuity had deteriorated again to hand movements in the nasal upper quadrants only. The tumour was once more aspirated and vision improved (VAL 6/12, J.14, VAR 6/36, J.18).

She was twice admitted to hospital in the next 18 months on account of episodic visual failure but on each occasion this improved spontaneously without operative interference. Her condition has since remained stationary and when seen five years after the operation she was well and active with good vision (VAL J.1, VAR J.6) and fields full to confrontation. Her mental state was normal.

Case 10 (U.O.H. 26618).—C.M., a 60-year-old woman, was noticed by her family and friends to be becoming nervous and irritable. Although normally a capable and placid person she became easily upset by trivialities such as whether her family came home later than usual. Small household matters, such as times of meals, caused her undue concern and she complained of constant tiredness. Her symptoms were ascribed to the strain of air-raids and to worry about her husband who was on active service. A rest in the country was advised and she seemed to improve. Soon afterwards, however, she found she was unable because of failing memory and increasing lethargy to manage the large amount of voluntary war work she was engaged in and even her correspondence was neglected. The letters to her husband, formerly cheerful and informative, became short and disjointed, she was irritated by the servants, forgot what she was doing, had to write everything down, and could concentrate on a subject for only a few moments. Her family noticed that although she could recall and describe events which had occurred years

before, daily happenings were often forgotten by the evening. She rested often and fell asleep at the slightest opportunity.

Some months later she began to lose her way about the house, although she could still recognize faces and carry on a reasonable conversation. She complained of stiffness in the legs and was from time to time incontinent of urine. There was slight headache but no visual symptoms and the total length of history was one year. Her menstrual history was normal and she had two children.

On examination at that time she could remember neither the year nor her whereabouts. She understood and obeyed simple commands such as "close your eyes", but more complicated instructions were ignored. She had no idea of current events and could not do simple mental arithmetic.

She was unable to recognize a photograph of her son although she did recognize her husband. Speech was slow and deliberate and she would often change the subject in the middle of a sentence or break into poetry. She was able to name only one of six common objects and perseverated frequently. She did not know how to hold a fountain pen or a match. Her mood was apathetic but cheerful and she was always gracious and courteous when spoken to.

Physical examination revealed a normally proportioned woman who was not wasted and did not look ill. There were no signs of endocrine abnormality, hair, skin, and sexual development being compatible with her age.

In the central nervous system there was no anosmia and the optic discs were rather pale but not definitely abnormal. Vision was J.2 bilaterally and fields were full to confrontation. Field charting was impossible due to lack of cooperation. In the limbs there was weakness and some increase in tone more marked on the left side. Reflexes were all brisk, left more than right, and plantar responses were unobtainable. There was a marked tremor on movement of either hand and no sensory deficit. Blood pressure was 170/100 mm. Hg.

Investigations.—A skull radiograph showed a calcified tumour above the sella, which was normal in size.

A lumbar puncture showed clear fluid at normal pressure, with protein, 60 mg., and no cells.

A ventriculogram showed that the right ventricle was entered easily, and pressure was 15-17 mm. of water. Both lateral ventricles were greatly dilated, the right more than the left. The third ventricle was not well filled but a large calcified tumour was seen projecting into it.

Operation and Progress.—The tumour was approached through the right lateral ventricle after reflection of a frontal flap. The right foramen of Munro was distended and a bluish cyst projected through it. After further exposure the cyst was dissected free off the walls of the third ventricle and removed although a portion of it had to be left behind.

Following the operation there was little change in the patient's physical or mental state. She was able to live at home but six months later was readmitted for further aspiration of the cyst. Vision at that time was R J.12, L J.10; all limbs were spastic with increased reflexes and extensor plantar responses.

She was admitted for the last time two years after the onset of her illness. There was little change in the physical signs though she had gained some weight. Vision was J.12 right and left. Ventriculography showed enormously dilated lateral ventricles but no filling of the third ventricle.

An attempt was made to remove the tumour radically but she developed pulmonary oedema and died soon afterwards. The diagnosis was confirmed histologically.

Case 6 (U.O.H. 266283).—H.W., a woman aged 67 years, previously an energetic housewife of average intelligence, was noticed by her husband to be losing her memory. She did not seem able to concentrate on a subject for more than a few seconds and wandered aimlessly about the house forgetting what she had meant to do. She also tended to fall asleep many times during the day and continually complained of tiredness.

Soon afterwards she began to notice visual blurring which at times was severe enough to restrict her vision to hand movements while at other times she could see to read. She consulted an ophthalmologist who found visual acuity reduced to hand movements and pallor of both discs. Field charting showed bilateral central scotomata. Skull radiographs were normal.

No diagnosis was reached and she continued at home gradually losing both her sight and her senses, until nine months from the onset when she was admitted to hospital because she refused to eat or drink.

She had had only slight headache but she complained of increased sensitivity to cold.

There were no significant features in her past or family history. Menses had been normal, and she had borne four children.

At the time of admission to the Churchill Hospital under Dr. Ritchie Russell, she appeared profoundly demented. She lay motionless in bed moaning feebly and resented any attempts to speak to her. She was unable to feed herself and was incontinent of urine.

She knew the names of her relatives but was unable to name the hospital or the year. She thought she was at home in bed, that she was 40 years old, and that both her parents were alive (although they had been dead for 20 years). She had no knowledge of current events and could not attempt tests of mental arithmetic. She could retain five digits forwards but not backwards. She frequently dropped off to sleep during the day and when roused appeared even more confused than usual. There were, however, lucid intervals in which she would converse sensibly, knew she was in hospital, and gave her age and address correctly. She never smiled and her mood was one of apathy and deep depression.

Physical examination revealed a pale and dehydrated woman of normal proportions. The skin was colourless and atrophic, the hair thin, and the sexual development compatible with age.

She was able to appreciate hand movements only in all parts of the field. Both optic discs were atrophic and pupils reacted sluggishly to light. There were no other abnormal signs. Blood pressure was 110/60 mm. Hg.

Investigations.—The cerebrospinal fluid was under normal pressure and was without clear cells. Protein level was 60 mg. per 100 ml., total serum proteins 6·1g./100ml. (albumin 2·85, globulin 3·25).

Haemoglobin was 17·5 g./100 ml., white blood cells 7,000/c.mm. (normal differential), and blood sugar (fasting) 83 mg./100 ml.

An insulin sensitivity test showed increased sensitivity by a blood sugar level of 38 mg./100 ml. half hour after 1·5 units of insulin.

Blood urea and electrolytes were normal and the blood cholesterol 195 mg./100 ml.

Urinary volume was 1,500 ml./day, with an average neutral 17-ketosteroid excretion of 2·5 mg./24 hours.

A skull radiograph showed that the dorsum sellae was thin, without abnormal calcification.

For a lumbar air encephalogram the patient was uncooperative. No definite abnormality was seen, the lateral ventricles were normal, but the third ventricle did not fill well.

Progress.—Two weeks after admission she developed fever and neck stiffness and was found to have a pleocytosis (500 polymorphs/c.mm.) of the cerebrospinal fluid. She was assumed to have a meningitis following the initial lumbar puncture although no organisms were isolated. Treatment with penicillin and streptomycin appeared to have some effect but repeated relapses occurred. Meanwhile her mental and visual state continued to deteriorate and she soon became quite blind. Treatment with cortisone and with thyroid was ineffective and she was transferred after six weeks to a chronic hospital. There she died one year after the onset of symptoms and post-mortem examination showed a large cystic craniopharyngioma which occupied the anterior part of the third ventricle and which histological examination showed to be infiltrated with polymorphs and chronic inflammatory cells. There was slight hydrocephalus, and no signs of meningitis.

Case 11 (U.O.H. 966116).—J.S., an active and successful farmer of 57, noticed the onset of frontal headache following a heavy blow on the head sufficient to knock him unconscious for a few minutes.

From then onwards he felt continually tired and gave up part of his work. His wife also noticed that he was excessively forgetful and that he tended to drop off to sleep after meals. A doctor was consulted and a period of bed rest was advised. His memory seemed to improve for a time, then deteriorated again. He was depressed, sleepy, and disinterested and had to give up his work entirely. He retired to bed at home but shortly afterwards lost all his memory for farming matters, could not recall the date or time, and began to vomit. He refused to eat or drink and his admission to hospital was arranged.

His past health had been normal in every way and he was married with one son.

On examination in hospital he was drowsy and disinterested and his speech was rather slurred. He was unable to say whether he was in hospital or in church and was surprised to hear that the war had ended some years before. He could not remember how he had come to hospital or how he had spent the past few days but remembered the names of his family and the fact that he was a farmer. He was extremely distractable, continually looking round for an opportunity of changing the conversation and tried to avoid questioning by closing his eyes. When pressed for an answer he would say he was a soldier, had been wounded and wanted a rest, and then would change the subject abruptly. He was unable to attempt tests of mental arithmetic but could obey simple commands and was able to read, write, and name simple objects. His vocabulary was normal, he was apathetic, and had no insight into his condition.

Physical examination revealed a well-nourished, normally-proportioned man with a high colour and no evidence of endocrine abnormality. In the central nervous system there was no anosmia, corrected vision was L 6/24, J.6; R 6/12, J.6, and fields were full to confrontation. The optic discs were normal and there were no other relevant findings. Blood pressure was 140/80 mm.Hg. A subdural haematoma was suspected.

Investigations.—In the cerebrospinal fluid (ventricular fluid) pressure was 120 mm., with no cells, and protein 130 mg. per 100 ml.

A sugar tolerance test was normal.

An arteriogram showed evidence of some hydrocephalus but none of displacement.

A ventriculogram showed moderate hydrocephalus of the lateral ventricles, and a space-occupying lesion on the floor of the third ventricle arising from the hypothalamic area.

Operation and Progress.—A ventriculocisternostomy was performed, and following this there was no immediate improvement in the mental state. The patient was disorientated and amnesic for two days after the operation and thought he was in Glasgow. Drowsiness was more marked than before the operation. A few days later, however, he improved, became quite alert, cheerful and talkative, although still disorientated and confabulating. He was well enough for discharge after a month. For a further three months he remained confused, incontinent, and bedridden at home but then suddenly and dramatically improved, resumed his farming interests, managed his accounts, drove his car, and led a comparatively normal life. He was not incontinent, was free from headache, walked steadily, and his memory served him well. He remained in this state for a year but then drowsiness, memory disturbance, and vomiting returned. He became muddled and incontinent but there was no headache or visual disturbance. He returned to hospital where the findings were the same as those on the previous admission. The tumour was needled, found to be cystic and 60 ml. of yellow fluid was withdrawn.

There was transient improvement for a few days, but he then became drowsy again and finally died after a period of coma.

At necropsy the tumour proved to be a craniopharyngioma. The liver showed extensive cirrhosis.

Case 5 (U.O.H. 234340/57).—L.S., a 56-year-old housewife, complained of intermittent frontal headache which was ascribed to hypertension until her family began to notice progressive mental deterioration. She was

unable to remember her shopping list, neglected her home and personal appearance, and at times became confused as to her whereabouts. She was occasionally incontinent of urine and on some days appeared drowsy and apathetic, while on others she seemed normal and alert. About this time she had a number of attacks of unconsciousness of sudden onset and lasting about 10 minutes. During these seizures she was limp all over and was incontinent of urine. Sometimes the arms jerked. Shortly afterwards she was admitted to hospital as a cerebral tumour suspect. At no time was there any complaint of visual loss.

In her youth she had enjoyed good health and was married but childless. Twelve years previously she had suffered transient right hemiparesis with dysphasia, from which she made a full recovery. It was noticed just before admission that her speech had again deteriorated and that she had difficulty in finding the appropriate word.

On examination she was fully conscious but could not remember the date or the name of the hospital. She was easily flustered and confused and could not cooperate in mental testing. Her mood was apathetic and she never spoke spontaneously to her neighbours in the ward or to the nursing staff. She was incontinent of urine. She could respond to command and speech and vocabulary were normal, although she made a few mistakes in naming common objects.

Physical examination revealed a normally proportioned woman with some facial hirsutes but no other endocrine abnormality. The sense of smell could not be tested but the fundi were normal. The pupils were large and reacted sluggishly to light. Visual acuity was reduced but was not recorded. There was a left homonymous hemianopia and slight weakness in the left side of the face. The remaining cranial nerves were normal. In the limbs there was slight weakness of the left arm and leg but no reflex change or sensory loss. The blood pressure was 170/100 mm. Hg.

Investigations.—A skull radiograph showed erosion of the dorsum sellae with suprasellar calcification on both sides of the midline.

A right carotid angiogram showed that the pericallosal artery was slightly elevated and displaced to the right in the anterior part.

The Sylvian group of vessels were elevated. A ventriculogram showed marked dilatation of the lateral ventricles. The anterior part of the third ventricle was elevated and displaced to the left by a mass which extended almost to the foramen of Munro.

The cerebrospinal fluid was faintly turbid but colourless with no cells, and protein, 70 mg./100 ml.

An EEG gave a dominant rhythm of 7 to 8 c/s with random delta waves at 1-2 c/s in all leads. No consistent focus or asymmetry was present.

Operation and Progress.—The tumour was approached after a right frontal flap and elevation of the frontal lobe. A large purple mass was found presenting on the medial side of the right optic nerve and displacing it upwards and outwards. The mass was incised and the contents removed piecemeal. It was found to extend posteriorly under the right optic tract. As much as possible of the capsule and contents were removed.

Post-operatively the patient appeared a little more alert but remained grossly demented and the left hemianopia and mild left hemiparesis were unchanged. Sight showed some subjective improvement and she was able to walk around the ward. Seizures were controlled by phenytoin.

Three months after operation, however, she again became bedridden and demented and died at home. There was no necropsy but the diagnosis was confirmed histologically on tissue removed at operation.

Case 20 (U.O.H. 3096/37).—C.L., an unmarried woman, had an uneventful medical history until the age of 66 when she noticed that she was having difficulty in reading the number plates on motor-cars. This improved for a time after a visit to the oculist but showed a further sudden deterioration five months later. She noticed that vision to the side was particularly affected.

About this time a number of other symptoms appeared. She had occasional headache, she began to fall asleep during the day whenever she sat down, and felt constantly tired; she was excessively thirsty and her relatives noticed a rapid decline in her mental faculties. Although previously an alert and intelligent woman, she became very absent minded and failed to recognize her friends. She was apparently quite unaware of the time of day, although she talked sensibly about the distant past. She neglected herself and forgot to go shopping, and when her sister came to stay and look after her, she mistook her for her mother who had been dead for 20 years.

In the past she had a normal menstrual history and passed the menopause at the age of 48. From the ages of 30 to 34 she suffered from frequent severe headaches accompanied by almost total loss of sight in the whole visual field for half an hour. Another episode of headache and visual failure occurred 10 years later but again passed off in a year or two leaving her free from symptoms. She came of a long-lived family, and there was no history of migraine.

When seen three months after the onset of mental symptoms, she was pleasant and cooperative but yawned frequently and tended to fall asleep if conversation lapsed. She was hopelessly confused about the place and date and did not know how long she had been in hospital. Memory for recent events was particularly poor; although she was told the name of the doctor she was unable to recall it 30 seconds later and had constantly to be reminded. Tests of mental arithmetic were performed slowly but accurately, but she was easily distracted. Her mood was normal.

Physical examination revealed a well-nourished woman, looking rather younger than her years. The skin was pale, smooth, dry, and hairless and showed erythema ignis over the shins. Scalp hair was normal but pubic hair was sparse and axillary hair absent. The sexual organs were normal. In the nervous system there was anosmia on the left, hyposmia on the right. Acuity was VAR 3/6, J.4, VAL 3/12, J.12, and field charting showed a scotomatous type of bitemporal hemianopia, the scotomata ending sharply at the vertical meridian.

Fundi were normal and both pupils reacted sluggishly. There were no other abnormal signs apart from conduction deafness in the right ear. Blood pressure was 140/90 mm. Hg. Average daily urinary volume was 3 litres and was markedly reduced by pituitrin. She vomited occasionally and had attacks of uncontrollable shivering unaccompanied by change in temperature.

Investigations.—A glucose tolerance test showed, fasting, 95 mg./100 ml., three-quarters of an hour after 50 g. glucose, 200 mg., and two hours after 50 g. glucose, 154 mg.

The cerebrospinal fluid was clear at a pressure of 70 mm. with cells 2/c. mm., protein 50 mg. per 100 ml. The Lange curve was 0000000000 and the Wassermann reaction negative.

A radiograph of the skull showed slight erosion of the dorsum sellae but no other abnormality.

An encephalogram showed a tumour mass projecting into the anterior part of the third ventricle.

Operation and Progress.—The tumour was approached by the right subfrontal route. The chiasma was post-fixed, the pituitary stalk was swollen, and a solid portion of tumour could be seen between the right optic nerve and the internal carotid artery. The tumour was circumscribed, firm, and homogeneous. A biopsy was done but no removal was attempted. The diagnosis of craniopharyngioma was confirmed histologically.

After the operation there was a period of peripheral circulatory collapse, but the next day she improved and a week later vision was left J.2; right, J.4. Polyuria persisted but she was correctly orientated and carried on a sensible conversation. Memory was much improved.

Over the next six months her mental state returned to normal and she was able to lead an active life, although still handicapped by the visual field defect, and by pains in the small joints of her hands.

She died four years after the operation of a cerebral haemorrhage.

Endocrine Abnormalities

A summary of the relevant history and findings in the endocrine system is set out in Table I. Evidence of severe, long-standing hypopituitarism as shown by small stature or failure to achieve sexual maturity only occurred in one patient, a small, mentally retarded woman with primary amenorrhoea and absence of secondary sexual characteristics.

Ten patients exhibited a milder degree of pituitary or hypothalamic disorder which had been present for some years. Common symptoms were lassitude, decreased tolerance of cold, irregular menstruation, diminished libido, weight gain, polyuria (which was sometimes episodic), and subnormal beard growth. This was confirmed on physical examination by the finding of pale, finely-wrinkled skin, brittle, sparse body hair, and a plump, relatively youthful appearance. However, 13 patients had no definite endocrine symptoms and had no abnormal signs.

Potency was little affected; of the total group of 24 patients, 20 were married and 16 had children. None of the patients had hypertension. In 18 the blood pressure was normal and in three the systolic pressure was below 110 mm. Hg. Two patients were known to have suffered previously from hypertension but had normal values.

Biochemical investigations were not performed on all patients and gave little additional information. Fasting blood sugar values were low normal, tolerance curves flat; ketosteroids were within the range of normal for age.

Other Clinical Features

There were few other abnormalities in the central nervous system. Anosmia occurred in five patients, but three were confused at the time of examination. One patient had a lateral rectus palsy. There were no changes in the limbs apart from one patient who had symmetrically increased reflexes and extensor plantar responses.

Three patients suffered from seizures, two were grand mal in type with convulsive movements of all limbs. One had falling attacks with sudden loss of power in the legs and momentary loss of consciousness.

Cerebrospinal fluid was examined in 19 patients. In five it was normal, in 10 the protein content was raised from 50 to 100 mg./100 ml., and in four from 100 to 170 mg./100 ml.

In three patients there were recurrent episodes of sterile meningitis with polymorphonuclear response in the cerebrospinal fluid. In two the meningitic episode occurred post-operatively and in one following a lumbar puncture. No organisms were grown despite repeated cultures.

Skull radiographs showed abnormal calcification above the sella in 13 with moderate or great enlargement of the sella in six.

Follow-up

It was possible to obtain information about 23 out of the 24 patients in this series, and the details are set out in Table II. Two treated and three untreated patients were alive 10 or more years later although two of these were severely demented. Three died in the immediate post-operative period in a state of peripheral circulatory failure. Six died within a year of operation and two within five years of operation.

Discussion

The Visual Symptoms.—It is clear from the number of cases in this series and from other reports (Pennybacker, 1949; Love and Marshall, 1950) that tumours of Rathke's pouch, although of developmental origin, may present at any time from

TABLE II

CLINICAL FEATURES, RADIOLOGICAL FINDINGS, AND SITE OF TUMOUR

Case No.	Sex and Age	Principal Clinical Features	Physical Findings	Tumour Site and Radiological Findings
1	Male, 55, married, 1 child	Visual failure, fluctuating, 4 years, moderate headache. Diagnosed as tobacco amblyopia	VAR J.10, VAL J.2, optic atrophy, bitemporal hemianopia (scotomatous). Wt. 160 lb., ht. 5 ft. 8 in., normal habitus, normal body hair. B.P. 140/80 mm.Hg.	Cystic tumour behind and medial to R. optic nerve, sella normal, no hydrocephalus
2	Male, 72, married, 5 children	Visual failure, fluctuating, 11 months, mild headache. Diagnosed as tobacco amblyopia. Excessive somnolence (episodic) 6 months, memory good	VAR J.8, VAL J.10, at times R J.8, L J.2 at times R no PL, L J.16, discs both pale, bitemporal hemianopia (depressional). Wt. 157 lb., ht. 5 ft. 9 in. B.P. 150/100 mm.Hg.	Cystic tumour beneath sella and optic nerve, normal sella radiologically
3	Male, 52, married, 2 children	Visual failure, fluctuating, 1 year, no headache	VAR 3/36, VAL 6/18, discs both pale, bitemporal hemianopia with central scotoma. Wt. 122 lb., ht. 5 ft. 5 in. B.P. 110/60 (previously 170/110) mm.Hg.	Almost solid tumour beneath chiasma and R. optic nerve, normal-sized sella, no hydrocephalus
7	Male, 57, married, 2 children	Visual failure, fluctuating, 6 months, slight headache	VAR 6/6, VAL 6/6 J.1, discs normal, L. homonymous hemianopia (incongruous with paracentral scotoma). Normal habitus. B.P. 150/90 mm.Hg.	Sella normal size
8	Male, 64	Seizures, visual hallucinations R. side, no headache	VAR 6/9, VAL 6/9, discs normal. Bitemporal hemianopia (depressional). Normal habitus	Sella normal size
9	Male, 61, married, 3 children	Visual failure, progressive 6 months R, 6 years L, no headache	VAL no PL. VAR HM, optic atrophy, temporal hemianopia R, blindness L. Normal habitus. Wt. 140 lb., ht. 5 ft. 5 in. B.P. 120/95 mm.Hg.	Cystic tumour extending frontally, sella normal size, erosion sphenoidal wings, no hydrocephalus
12	Female, 47, married, never menstruated	Mental slowing, no visual symptoms, no headache	VAR no PL. VAL 3/30 J.16, optic atrophy, L. temporal hemianopia with blindness R. Wt. 100 lb., ht. 5 ft. 1 in. Skin fine, smooth, pale, hair thin, no axillary or pubic hair, vagina hypoplastic, breasts very small. B.P. 80/60 mm.Hg. P. 60	Solid tumour extending frontally, gross enlargement of sella
13	Male, 50, married, 1 child	Visual failure progressive 2 years, severe headache	VAR J.8, VAL J.20, optic atrophy, bitemporal hemianopia with lower nasal scotoma R. Wt. 150 lb., ht. 5 ft. 6 in. B.P. 140/95 mm.Hg.	Cystic intraventricular tumour abutting on chiasm from above and behind, sella small
14	Male, 67, married, 1 child	Visual failure slowly progressive L>R 10 years, no headache	VAR J.8, VAL HM, optic atrophy, bitemporal hemianopia and loss of upper nasal quadrant L. Delicate skin, hair thin	Sella moderately enlarged
15	Female 51, unmarried, menses normal	Mental deterioration, no visual symptoms, moderate headache	VAR 6/18 J.7, VAL 6/36 J.10, discs normal, small haemorrhage R. fundus, full to confrontation, charting impossible. B.P. 150/90 mm.Hg.	Cystic tumour above chiasm, sella normal size, marked hydrocephalus
16	Male, 63, unmarried	Visual failure, memory loss progressive 1 year, moderate headache	VAR 6/9 J.16, VAL 2/60 J.20, bilateral papilloedema, bitemporal hemianopia + loss of L. lower nasal quadrant. Wt. 210 lb., ht. 5 ft. 10 in. Hair fine, brittle, axillary hair absent, genitalia normal	Cystic tumour, sella normal in size. Vision unchanged post-operatively, discs flat, moderate hydrocephalus
17	Male, 42, married, 3 children	Visual failure R. eye only, fluctuating R. 8 months, slight headache, diagnosed as tobacco amblyopia	VAR 6/60, VAL 6/6, discs pale, bitemporal hemianopia, scotomatous. Normal proportions. B.P. 120/80 mm.Hg. (previously hypertensive)	Cystic tumour under posterior border of chiasm, sella normal in size, no hydrocephalus
18	Female, 44, married, no children, menses irregular, menopause at 39	Visual failure, progressive L, R 4 months, no headache	VAR 6/6, VAL 6/18, discs normal, bitemporal hemianopia, scotomatous. Ht. 5 ft. 5 in., thin, skin pale. B.P. 150/100 mm.Hg.	Cystic tumour between optic nerves and under R. nerve and anterior border of chiasm, moderate enlargement of sella, no hydrocephalus
19	Male, 40, married, 1 child	Visual failure, progressive 7 years, moderate headache	VAR 1/24, VAL P.L., optic atrophy, bitemporal hemianopia + loss of lower nasal quadrant L. Small stature, pubic hair scanty, testes small, smooth skin. B.P. 110/70 mm.Hg.	Cystic tumour, sella normal size
21	Male, 53, married, 3 children	No headache, libido diminished 3 years	VAR 6/6, VAL 6/6, discs normal, full fields, tall, normally proportioned. B.P. 130/80 mm.Hg.	Sella much enlarged
22	Female, 62, married, 2 children, menses normal, menopause at 49	Visual failure, progressive 18 months, no headache, lassitude	VAR J.14, VAL J.1, R. disc pale, L. normal, bitemporal hemianopia R. complete, L. depressional, normal habitus. B.P. 160/90 mm.Hg.	Sella enlarged
23	Female, 51, married, 3 children, menopause at 48	Visual failure, progressive 6 months, moderate headache	VAR 6/18 J.16, VAL 6/18 J.12, discs normal, bitemporal hemianopia (depressional). Wt. 133 lb., ht. 5 ft. 1 in. B.P. 170/110 mm.Hg.	Sella greatly enlarged
24	Female, 40, married, 3 children	Visual failure, progressive 6 months, slight headache, loss of energy, memory poor, periodic somnolence for 1 yr.	VAR 6/60 J.16, VAL 6/12 J.4, optic atrophy, L. lower temporal defect, R. central scotoma, Wt. 170 lb., ht., 5 ft. 1 in., dry skin. B.P. 130/80 mm.Hg.	Sella normal, suprasellar calcification, cystic tumour arising from pituitary stalk and extending into third ventricle

childhood to old age, and that in one patient in four symptoms first occur after the age of 40 years. The clinical features at this age differ markedly from those in younger patients, but visual disturbance remains a common symptom. It may be undetected because in the early stages it may affect only one eye, because the patient may be unable to give an adequate account, or because of the absence of abnormality on retinal examination. Occasionally vision is lost abruptly and a patient has been described in whom total or permanent blindness occurred in a few hours (Wertheimer and Corradi, 1957), a sequence of events suggesting a vascular occlusion. Much more commonly a slow decline in visual acuity affecting one or both eyes takes place over months or years before the patient seeks advice. The average for the present series was 27 months.

The retinal appearances are often misleading; although a proportion of cases show optic atrophy and others a questionable pallor of the discs, in many there is no abnormality. Papilloedema is common in young patients with third ventricular obstruction but rare after 40 years of age. Of 100 cases of all ages reported by Love and Marshall (1950) papilloedema was present in 28 and optic atrophy in 21. In the series of Wagener and Love (1943), the discs were normal in six, pale in nine, atrophic in six and oedematous in eight, all patients with papilloedema being under 25 years of age. There was no correlation between the presence of optic atrophy and the situation of the tumour. The ophthalmoscopic findings in the present series and in these and other reports (Wertheimer and Corradi, 1957) are in general agreement.

Much more consistent changes are found in the visual fields, and they emphasize the importance of quantitative perimetry in diagnosis. Many different varieties of field change have been described, among them bitemporal hemianopias, homonymous hemianopias, concentric contractions of fields, and central or paracentral scotomata. Bitemporal defects, usually asymmetrical, are the commonest finding, occurring in about half the patients, homonymous defects in about a quarter (Love and Marshall, 1950). The frequency of central scotomatous defects is very variable but in some series they occurred in about a third of patients, usually in combination with peripheral field changes (Wagener and Love, 1943).

The position of the tumour as far as can be determined by clinical, radiological, and operative findings, bears no constant relation to the type of field defect. Because of variations in size and in site of origin and because of inconstant fixation of the chiasm, no part of the optic nerve, chiasm, or tract is particularly vulnerable. It might be supposed that central scotomata would be produced by anteriorly placed tumours affecting the optic nerves, bitemporal hemianopias by tumours at the chiasm, and homonymous defects by tumours behind the chiasm. The most that can be said is that anteriorly placed tumours are usually associated with bitemporal defects and posteriorly placed tumours, sometimes with homonymous defects, while central scotomas may occur with tumours in any situation (Wagener and Love, 1943).

Since one eye is usually more severely affected than the other the compressive lesion is probably towards one or other side of the chiasm rather than in its centre, and the finding in severe cases of one blind eye with a temporal hemianopia in the other is in accord with a lesion of the anterior chiasmal angle. Cases 9 and 12 in the present series, which presented this field defect, both had anteriorly situated tumours.

It has been said that in cases of bitemporal hemianopia the lower temporal quadrants are affected first, indicating a lesion affecting the chiasm from above (Hughes, 1954). In the present series, however, the upper and lower quadrants were affected with equal frequency. Nor was radiological enlargement of the sella associated with any particular type of field change. Scotomatous defects were as common as the depressional variety in the present series and this may be misleading unless the peripheral isopters are charted. These are seldom full and usually show some temporal indrawing. In scotomas near the fixation point there is usually a sharp demarcation at the vertical meridian which suggests a lesion of the fibres from the nasal side of the macula running in the postero-inferior border of the chiasm. Four such cases occurred. Operation in Cases 17 and 13 confirmed a tumour in this situation, but in Cases 1 and 18 the tumour was anterior to the chiasm in relation to the optic nerve.

Central scotomas were first reported by Critchley and Ironside (1926) and have been repeatedly observed since then. The suggestion has been made that they are caused by traction on the optic nerves as the chiasm is displaced by the tumour, or by angulation of the nerves at the optic foramina (Hughes, 1954). Scotomas may be found in association with both temporal and homonymous field loss. Of the four patients in this series who had central scotomas only two were operated on. In one the tumour was found under the chiasm and optic nerve on the side of the scotoma (Case 3) and in the other the tumour was pressing on the chiasm from above and behind (Case 24).

Both visual acuity and fields are subject to

remarkable fluctuations and these may give rise to diagnostic difficulty, especially when the field loss is central or centro-caecal. Three patients in the present series were thought to have tobacco amblyopia or retrobulbar neuritis because of a unilateral diminution of acuity recovering in a few weeks, and this mistake has been made before (Witt, MacCarty, and Keating, 1955).

Changes also occur in the visual fields and cases have been reported in which a bitemporal defect became homonymous (Holloway, 1935). Fluctuations in the visual state may be accompanied by hypothalamic changes, by the transient appearance of somnolence, polyuria, or memory disturbance, or sometimes by reversible EEG changes (Norstrand, 1955). The cause of these fluctuations is not clear. It may be due to variations in size of a cystic tumour, but it was also observed in tumours which were almost entirely solid (Case 3 of the present series). Local oedema is perhaps the likeliest explanation and is probably on a vascular rather than an inflammatory basis, since histological examination seldom shows any cellular infiltration of the tumour.

The Mental Symptoms.—The finding that over half the patients in this series suffered from impairment of memory and that eight patients presented the appearances of advanced organic dementia shows that mental symptoms are of considerable diagnostic importance although they have been comparatively neglected in the literature.

Farnell (1911) described a pituitary adamantinoma in a woman of 43. She suffered from episodes of amnesia and extreme sleepiness, and was often confused and disorientated. Impairment of memory and periods of drowsiness were noted in a woman of 27 reported by Critchley and Ironside (1926). Necropsy confirmed the presence of a craniopharyngioma but there was no hydrocephalus. In a patient of Beckmann and Kubie (1929), a man of 43, a Korsakow delirium with amnesia and confabulation occurred post-operatively. Cushing (1930) noted personality change in one patient associated with a period of somnolence, polyuria, and emotional negativism, all of which he regarded as due to hypothalamic damage. Dott (1938) described two patients aged 37 and 42, in whom amnesia and disorientation were prominent symptoms. One of these had a tendency to emotional lability and disinhibition. Of 100 cases reviewed by Love and Marshall (1950), four had psychiatric features, consisting of memory loss, confusion, defective judgment, and episodes of mania. The changes were thought to be due to pressure on the frontal lobes by the tumour. Seizures occurred in four patients and in two there was an uncinate aura.

Comprehensive tests of mental function were undertaken by Williams and Pennybacker (1954) in four cases with tumours in the region of the hypothalamus. Three were craniopharyngiomas, and the patients showed marked defect of memory and learning with confusion and confabulation, but preservation of other features of intellect and judgment. The authors showed that the amnesia was probably the result of a local hypothalamic lesion and was independent of raised intracranial pressure. In a review of patients with craniopharyngioma, 72% of patients with growths involving the third ventricle showed some memory impairment but none of the patients in whom the tumour was further forward. The most marked changes were found in elderly patients.

Norstrand (1955) reported the clinical features of six patients over the age of 40 with craniopharyngiomas. In four there were mental symptoms; one was depressed, one uncooperative and apathetic, one confused and disorientated, and one had a period of abnormal behaviour post-operatively. Depression was noted in two out of 65 cases reviewed by Wertheimer and Corradi (1957) and was accompanied by headache and loss of weight. Memory changes were not recorded but somnolence was common (22%), one patient having attacks of irresistible yawning. The basal metabolic rate was normal. Tiberin, Goldberg, and Schwartz (1958) reported two cases aged 60-65 with advanced organic dementia. One had seizures and some features of hypothalamic disorder, and in the other the only localizing sign was optic atrophy.

There is a marked similarity in the case histories of the mentally affected patients in this series. In all, the earliest symptom was a defect of recent memory often fluctuating and due to a disturbance of attention and of the interpretation and elaboration of sensory information. This loss of retentive capacity was associated with episodes of somnolence, confusion, disorientation, and sometimes with confabulation. Mental testing showed a disproportionate difficulty with tests involving the repetition of stories after a short interval, the retention of new impressions, and the ability to learn new habits. Tests of immediate recall such as the repetition of a number of digits were performed much more easily. The patients appeared more severely disturbed in hospital than at home because of their inability to comprehend new surroundings or new faces. They were often difficult to rouse from sleep but once awakened were cooperative but extremely distractable. Vocabulary and distant recall were usually preserved. Social behaviour remained appropriate.

More severely affected patients showed in addition

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to the memory defect a general progressive deterioration in intellect with narrowing of interest, neglect of personal appearance, apathy, and emotional lability, which differed in no way from the dementia seen in many types of degenerative brain disease. This degree of mental disturbance occurred mainly in elderly patients and was associated in all but one case with considerable dilatation of the lateral ventricles. There was less tendency to fluctuation than in the younger patients. The difficulties of diagnosis in elderly patients may be great since the optic discs may be normal and visual acuity and field testing impossible because of lack of co-operation.

It seems likely that the early memory disturbance described above is due to a lesion of the hypothalamus or of its connexions with the hippocampal system (Russell, 1959). Protracted cases of Wernicke's encephalopathy, which usually exhibit clouding of consciousness and amnesia in addition to ocular abnormalities, show consistent vascular changes in the mamillary bodies and around the third ventricle and aqueduct (Gamper, 1928; Campbell and Biggart, 1939; Meyer, 1944). Furthermore, bilateral removal of the hippocampus produces a selective and profound amnesia for recent events, although other aspects of intelligence are spared (Scoville and Milner, 1957), and cases with bilateral hippocampal sclerosis or atrophy of the fornices without other cortical abnormalities are said to exhibit a similar state (Schenk, 1959).

Cairns (1952) showed that various lesions in the posterior part of the third ventricle, such as a tumour of the pineal gland or thalamus, post-operative oedema or damage to the upper brainstem, may produce not only amnesia but also various disturbances of consciousness, such as coma with tonic fits, petit mal seizures, hypersomnia, and akinetic mutism. He regarded the functions of consciousness, wakefulness, and memorizing as closely related and all controlled by a mechanism in the hypothalamus. This view is confirmed in the present series in which somnolence and amnesia appeared to go together, showing marked fluctuations both spontaneously and as a result of aspiration of a cystic tumour.

In the patient with a craniopharyngioma of the third ventricle reported by Cairns, Oldfield, Pennybacker, and Whitteridge (1941), a state of speechlessness and of muscular relaxation resembling sleep but with retention of purposive eye movements, was accompanied by a sleep-like EEG activity. The patient and the electrical record were dramatically restored to normal on aspirating the cyst, but there was complete amnesia for the akinetic period. Mental symptoms may show a similar sudden improvement after aspiration (Foerster and Gagel, 1933). Conversely, relief of intracranial pressure alone or by a ventriculocisternostomy frequently brings about no change in somnolence or in the mental state, indicating that raised pressure alone is not responsible (Cairns, 1952).

To explain the close relationship of disturbance of consciousness and memory with the upper brainstem it has been suggested that the hypothalamus by means of its thalamic connexions and by the fronto-hypothalamic fibres play a part in the laying down and facilitation of memory and learning patterns in the cortex and may constitute a mechanism which can quickly activate or suppress large areas of the cortex (Obrador, 1943). There is some localization even within the hypothalamus, amnesia being commoner in lesions such as craniopharyngiomas lying in the floor and sides of the ventricle than in those further forward, such as a colloid cyst of the third ventricle (Cairns and Mosberg, 1951).

On the other hand, some authors deny that amnesia has any localizing significance and state with some pathological evidence that it is related more to diffuse brain damage and in particular to the age of the patient (Bleuler, 1951; Carmichael and Stern, 1931).

Patients showing a global dementia with decay of all aspects of intellect and personality did not show marked fluctuations either spontaneously or as a result of treatment. Encephalography or ventriculography in these patients showed generalized dilatation of the lateral ventricles, sometimes with an obstruction to passage of air in the third ventricle, and the dementia probably resulted from cortical atrophy consequent on chronic obstruction of the third ventricle, in a brain already affected by age and arteriosclerosis. By a similar mechanism a tumour in the posterior fossa may sometimes present as an organic dementia in old age. It is significant that while circumscribed memory defect may occur in young patients (Williams and Pennybacker, Case 3), severe generalized dementia was seen, especially in the elderly. Extension of the tumour into the frontal lobes has been suggested as a factor, but was not apparent in the patients in this series coming to necropsy. Neither thyroid nor vitamin treatment has been effective even when the patient has been clinically hypothyroid (Case 8, present series).

General Observations

Since craniopharyngiomas are of developmental origin and may remain clinically silent until middle life or later, the rate of growth must be extremely slow or intermittent. Some cases in the present series were observed without treatment for periods

of 20 years without clinical or radiological change, and it is likely that a number remain symptomless and undiagnosed throughout life. A period of rapid growth with the compression of neighbouring structures may be followed by a prolonged period of inactivity during which no new symptoms develop. In two cases in the present series transient premonitory symptoms occurred during the third decade, in one a few weeks of polyuria and in the other a period of intense paroxysmal headache and vomiting. These episodes resolved without treatment and no further symptom occurred for 20 years. These striking fluctuations, which may affect visual, mental, or hypothalamic symptoms, make prognosis and the assessment of operative treatment very difficult, and suggest that surgery should be as conservative as possible, being restricted to those cases with signs of advancing chiasmal compression or of obstructive hydrocephalus. Since the bulk of a craniopharyngioma is usually cystic, an increase in size is probably brought about by an increase in volume of cyst contents, but there is little to show how this comes about. There is seldom any evidence of recent haemorrhage nor any microscopic evidence of inflammation of malignant change though this may occur (Wertheimer and Corradi, 1957). It is seldom possible to remove the entire tumour and the operative mortality of attempted radical removal is considerable (Critchley and Ironside, 1926; Grant, 1948). Since the reaccumulation of fluid after partial removal bears little relation to the amount of tumour removed, it may be wisest to carry out a limited excision of the cyst wall with aspiration of the contents and this procedure may be combined with ventriculocisternostomy. In Case 4 of the present series, repeated aspiration of the cyst alone was enough to abolish mental and visual symptoms for five years. It may be impossible to distinguish on clinical or radiological grounds between a craniopharyngioma and a pituitary adenoma, a difficulty which arises most frequently in middle-aged patients. The distinction is of more than academic importance in view of the favourable response of adenomas to *x*-ray therapy. The diagnosis is usually clear at operation, but since occasionally adenomas may be cystic and craniopharyngiomas solid, only histological examination is conclusive. The contents of the cyst may escape into the cerebrospinal fluid circulation either spontaneously or post-operatively and was the probable cause of the sterile meningitis in three patients in the present series. In three others the onset of symptoms was related to a head injury and this association has been noted before (Cushing, 1932).

In conclusion, it is evident that a craniopharyngioma should be considered in a patient of any age with symptoms suggesting compression of the chiasma, particularly when the visual field defect is asymmetrical, fluctuating, or scotomatous, and even when the skull radiograph shows no calcification (Love and Marshall, 1950). Craniopharyngiomas and tumours of the third ventricle should also be considered in the differential diagnosis of elderly patients with memory defect, somnolence or generalized organic dementia without obvious neurological signs, and particular note taken in such cases of any disturbance of visual acuity or fields.

Summary

The clinical features of 24 middle-aged and elderly patients suffering from craniopharyngiomas are described with particular reference to visual and mental symptoms.

Reduction in visual acuity or abnormality in visual fields occurred in all but one patient and there was much variation in the type and extent of field defect. Fluctuations in the visual state were a common and striking feature.

Mental changes were noted in half the patients and in some were the dominant feature. Six cases are described.

The natural history of the tumours and the mode of production of visual and mental symptoms are discussed.

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THE EFFECT OF AGEING UPON PHYSIOLOGICAL TREMOR

BY

JOHN MARSHALL

From the Academic Unit, Institute of Neurology, and National Hospitals for Nervous Diseases, Queen Square, London

It is a matter of common observation that the standard of motor performance declines with advancing years. There are several factors which may be associated with this. The conduction velocity in human peripheral motor nerve fibres has been shown to decrease by about 15% between the third and ninth decades (Wagman and Lesse, 1952; Norris, Stock, and Wagman, 1953). On the sensory side, the perception of vibration applied to the lower limbs is impaired in an increasing proportion of apparently normal people after the age of 50 years (Pearson, 1928; Cosh, 1953), and ischaemic and post-ischaemic paraesthesiae are likewise experienced less constantly (Poole, 1956). Reflex activity is also impaired more than can be accounted for by the changes in the efferent and afferent nerves. For example, Magladery, Teasdall, and Norris (1958) have shown that the latency of the flexor plantar response and of the superficial abdominal reflexes is greatly prolonged in old people. Central factors may also be involved, the reaction time, as one example, being demonstrably prolonged in older age groups (Welford, 1958).

Muscular movement in normal young adults is associated with a rhythmic tremor with a frequency of 10 cycles per second (c/s) (Marshall and Walsh, 1956; Halliday and Redfearn, 1956). In children, however, the tremor is slower, having a frequency of only 6 c/s (Marshall, 1959). This lower frequency in early life, and the knowledge that other nervous functions are affected by both maturation and senescence, made it of interest to study physiological tremor as age advances, first to define further the processes involved in the decline of motor performance, and secondly, to discover more about the nature of physiological tremor.

Materials and Methods

The method used to record the tremor was that described by Marshall and Walsh (1956). The patient held in his hand an accelerometer, double diode valve (Mullard DDR 100), the anodes of which are deflected by acceleration in one plane. The output from the valve upsets the balance of a bridge circuit, which was in turn fed through an Ediswan electroencephalographic amplifier to an ink writer.

The patient held the valve in the pronated hand with the upper limb fully outstretched and unsupported, so that the tremor recorded was that imparted by the whole of the upper limb. A mark on the valve cover ensured that the anodes were always held in the same plane. The recording was made and the age of the patient noted.

Subsequently, the frequency of the tremor was measured by laying a transparent cursor, ruled off in seconds, over the tracing and counting the number of waves in a second. Several examples were measured, and at the time of making the measurement the observer did not know the age of the subject.

Results

The tremor was recorded in 347 subjects in the age range 20 to 96 years inclusive. There were 165 males and 182 females; the number of subjects in each quinquennium is given in Fig. 1.

The subjects comprised persons working in the hospital, patients without obvious neurological disease in a geriatric unit, and people living in a local authority institution. There was no difference in the recordings obtained from each of these groups.

The frequency of the tremor of each subject is plotted in relation to age in Fig. 1. This shows that between the ages of 20 and 40 years the frequency of the tremor is around 9 to 11 c/s with no evidence of a decline in frequency during this period of years. From the age of 40 onwards, however, there is a steady decline in frequency, a decline which affects the whole of the sample population and is not confined to one particular group of subjects. In Fig. 2 the mean tremor frequency has been plotted against the mean age of the subject in quinquennial periods. This indicates that the mean frequency declines from just over 9 c/s at the age of 40 years to 6·5 c/s in the 70-74 age group and remains about this level between 70 and 90 years. There were only four subjects in the tenth decade, one aged 91, one 93, and two 97 years, all with a tremor frequency of 6 c/s. The observations in these upper age groups are too few to indicate whether the tremor frequency continues to decline after 70 years or whether it stabilizes

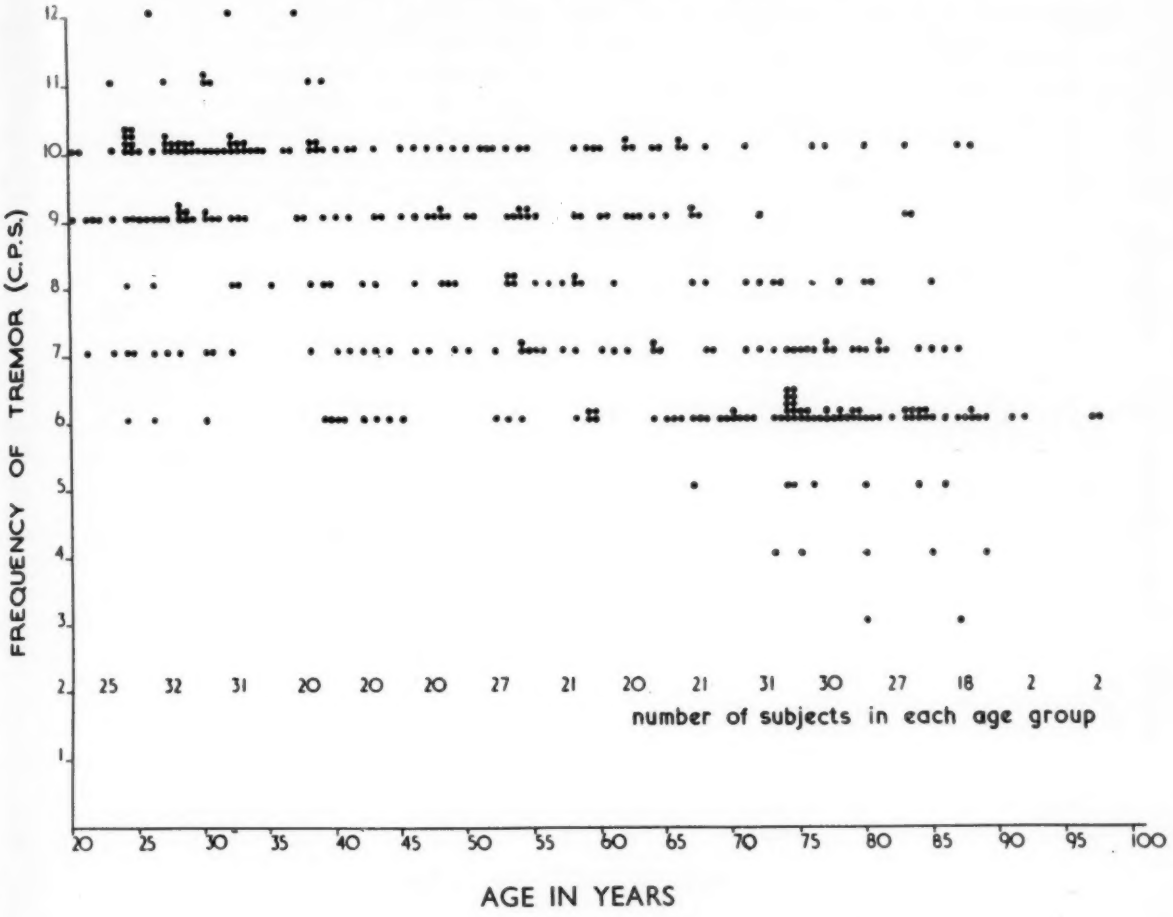

FIG. 1.—Graph showing the number of patients with each tremor frequency at each year of age.

at 6 c/s. Such indication as is provided by the data favours the latter possibility.

A regression line can be fitted to the data for the 40 to 97 year group of the equation $y = 10{\cdot}89 - 0{\cdot}053x$ where x is the age in years, and is shown in Fig. 2. The slope of this line differs significantly from that for the 20-39 year group which has the equation $y = 9{\cdot}014 + 0{\cdot}007x$ ($P < 0{\cdot}001$).

Discussion

These observations have shown that the frequency of physiological tremor, which is about 10 c/s in early adult life, declines significantly to a frequency of 6 c/s from the age of 40 years onwards. Though occasional patients had a tremor frequency below 6 c/s, there is a suggestion that the frequency stabilizes at 6 c/s and does not in general decline further. The decline in frequency affects all subjects, there being no suggestion of the emergence of two groups, one maintaining the 10 c/s tremor, the other developing a slower tremor. The slower tremor of old age is not, therefore, an abnormality afflicting certain persons, but is the normal accompaniment of advancing years. It must not be confused with the so-called senile tremor, in which the outstanding feature is a greatly increased amplitude. The exact nosological status of senile tremor is not clear, but it appears to be related to essential or familial tremor (Critchley, 1949).

The significance of the slowing of tremor frequency in old age cannot be considered without reference to the mechanism underlying the tremor of young adults. Marshall and Walsh (1956) were of the opinion that it is due to the muscles acting as a low-pass filter, and failing to follow stimulation frequencies higher than about 10 c/s reaching them from the nerve fibres. On the other hand, Halliday and Redfearn (1958), observing that the tremor frequency was reduced in patients with tabes dorsalis in whom there was clinical evidence of

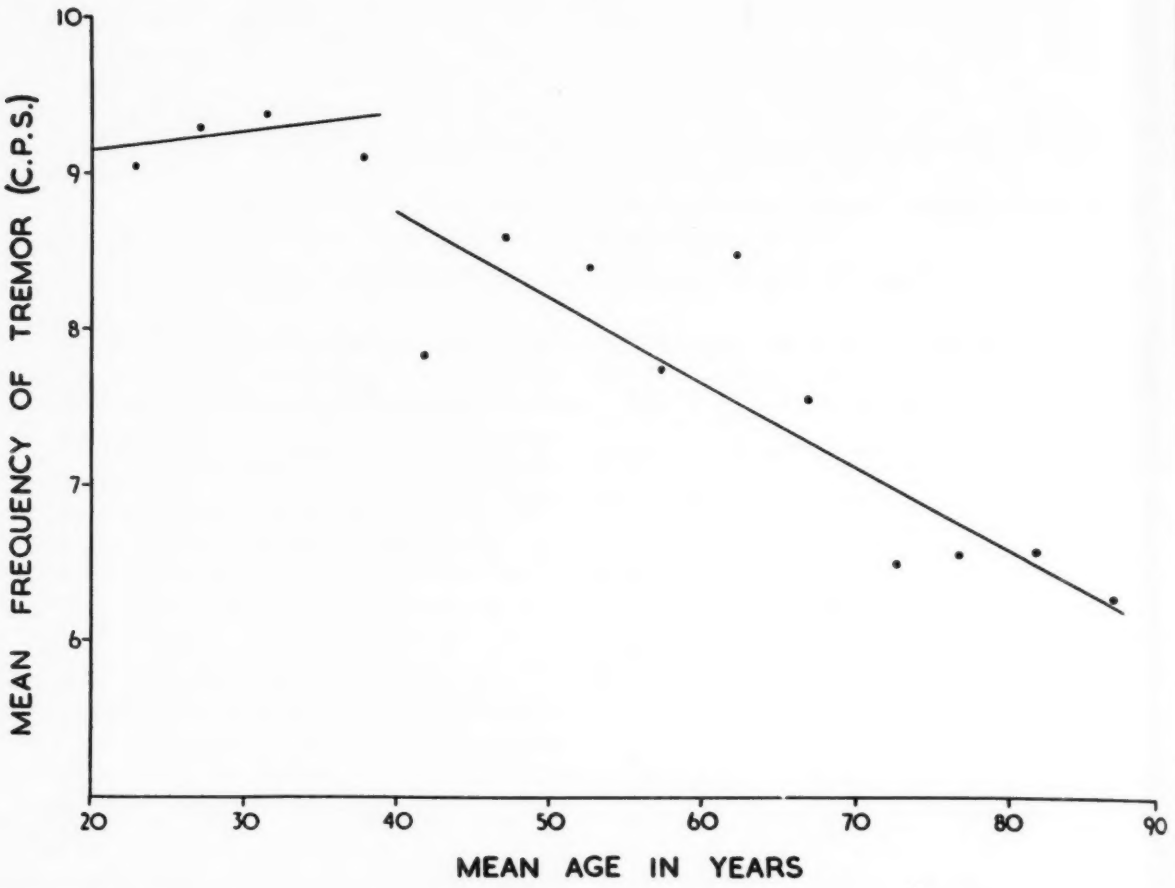

FIG. 2.—Graph showing the mean tremor frequency for each quinquennium with regression lines for the 20-39 and the 40-97 year groups.

damage to afferent nerve fibres, postulated that the normal tremor is due to the oscillation of impulses around the spinal reflex arc. If this latter explanation were the case, the reduced tremor frequency of old age might be attributed to changes in the reflex arc itself. The slowing in the conduction velocity in human motor nerve fibres of some 15% which has been demonstrated (Norris *et al.*, 1953) is, however, entirely inadequate to account for the reduction of tremor frequency from 10 to 6 c/s, even were it shown that there is a similar reduction in conduction velocity in the afferent limb of the reflex arc.

There is evidence that there is increasing synaptic delay with advancing years, at least in rats (Wayner and Emmers, 1958). This delay was not attributed to changes localized in the synapse, but to a decrease in the excitatory impulses reaching the synapse from other parts of the nervous system. That such influences may operate in man is indicated by the observation of Magladery and Teasdall (1958) and Teasdall and Magladery (1959) that lesions of the descending motor pathways prolong the latency of the stretch reflexes and of the superficial abdominal reflexes. These influences might also control the frequency of the oscillation in the reflex arc which has been suggested by Halliday and Redfearn (1956) as responsible for the normal tremor accompanying muscular movement. They might normally be absent in childhood, accounting for the lower tremor frequency up to the age of about 9 years (Marshall, 1959), appear during puberty, persist during early adult life, and decline after the age of 40 years or so. Speculation as to the source of these influences would have to take into account the fact that tremor at a frequency of 10 c/s accompanies reflex movements of the lower limbs in patients with complete interruption of the spinal cord pathways (Marshall and Walsh, 1956).

The development of the 10 c/s tremor occurs fairly abruptly at puberty, suggesting the replacement of one controlling influence by another rather

than the maturation of the same influence. The decline of the tremor frequency in later life is not so abrupt, but neither is senescence so dramatic an event as puberty. The suggestion that the tremor eventually appears to stabilize at a frequency of 6 c/s, the level from which it started in childhood, lends support to the concept of one controlling influence being replaced by another.

Summary

The tremor of the outstretched hand has been recorded in people between the ages of 20 and 96 years. The frequency declines after the age of 40 years from the 10 c/s in young adults to 6 c/s. The significance of the observations in relation to the mechanism of physiological tremor is discussed.

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QUADRICEPS MYOPATHY OCCURRING IN MIDDLE AGE

BY

J. W. ALDREN TURNER and K. W. G. HEATHFIELD

From the Department of Neurology, St. Bartholomew's Hospital, London

Cases of myopathy limited to the quadriceps femoris have occasionally been reported. We have had the opportunity of looking after the patient reported by Denny-Brown in 1939 and are describing the case again to emphasize the remarkably slow deterioration which has occurred over the 25 years since symptoms first appeared, together with another recent case with marked changes on muscle biopsy.

Case Reports

Case 1.—Mrs. L. W., aged 43, was admitted under the care of Dr. Denny-Brown in April, 1939, with a six years' history of weakness of both thighs not accompanied by pain. There was nothing relevant in the past history. Her husband had had syphilis which was adequately treated at an early stage and there was a family history of tremor but not of muscle weakness. On examination there was wasting of both quadriceps, especially of the vastus internus with severe weakness of extension of both knees, but there was no other wasting or weakness. The right knee jerk was absent, the left gave a flicker of response, the other reflexes were normal and there were no sensory changes. The blood Wassermann reaction was negative and the cerebrospinal fluid was normal. A biopsy of the vastus internus was carried out and the section (Fig. 1*a*) (Dr. Denny-Brown) shows small necrotic muscle fibres scattered throughout the muscle. The number of nuclei were greatly increased and the sarcoplasm stained deeply with eosin. In longitudinal section the necrotic changes extended throughout the length of the fibre. In places small fibres in a more advanced stage of degeneration were represented by bands of nuclei. The remaining muscle fibres were larger than normal and the majority showed nuclei in the substance of the fibre instead of the normal arrangement around the periphery. There was no inflammatory reaction.

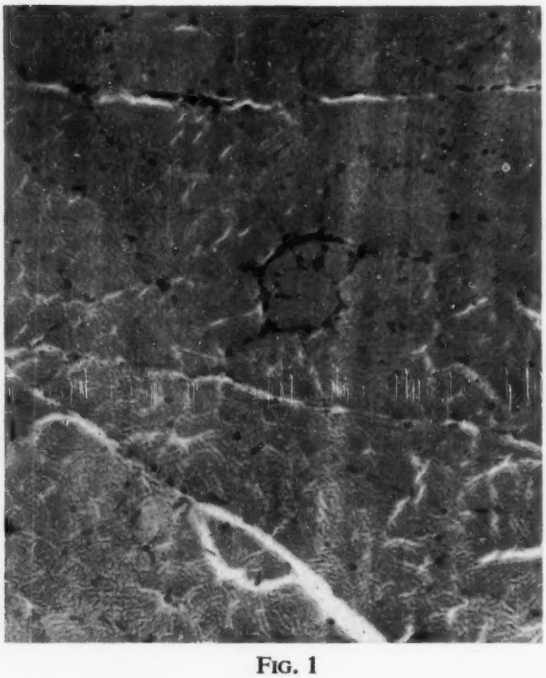

FIG. 1

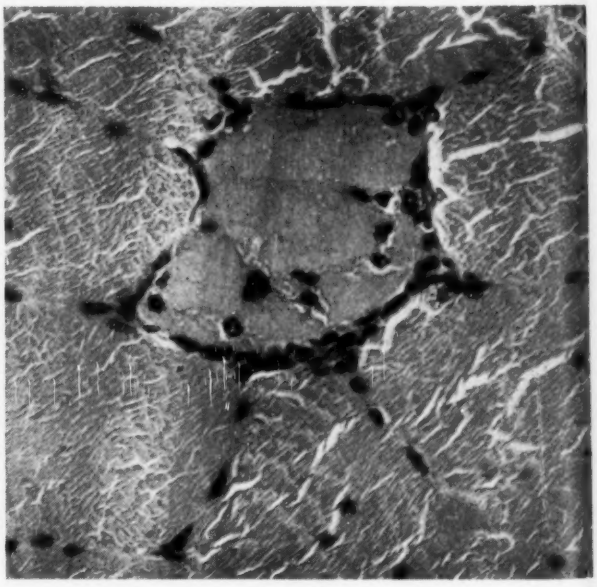

FIG. 1a

FIG. 1.—Case 1: Biopsy of vastus internus. ×125.

FIG. 1a.—Same section as in Fig. 1. ×400.

The patient was treated with glycine and attended the Out-patient Department at intervals and was readmitted in October, 1949. In the intervening 10 years the legs had become very gradually weaker and she had noted some weakness of the trunk muscles for about a year and slight weakness of the arms for two years. The menopause had occurred three years earlier. On examination, there was a small swelling in the mid-line of the thyroid which she said had been present for 20 years and which had been noted on her admission in 1939. There was slight wasting and weakness of both triceps with absent jerks, gross wasting and weakness of both quadriceps with absent knee jerks, and slight weakness of the hip flexors and extensors. Other muscles were of normal power except for slight weakness of the lower trunk muscles. The other reflexes were normal and there was no sensory change.

X-ray examination showed some antero-posterior narrowing of the trachea underneath the thyroid. The B.M.R. was 10%, the blood cholesterol level 182 mg. per 100 ml., and an E.C.G. normal. The thyroid nodule was removed on November 11, 1949, by Mr. Alan Hunt and histologically this showed thyroid tissue of low colloid content, together with two localized "adenomata". Biopsies of the right sterno-mastoid and left sterno-hyoid were made at the operation and these showed little abnormality apart from small areas in which the muscle fibres were atrophied and the interfibrillary connective tissue increased.

She has been seen at intervals up to October, 1959, and when re-examined then showed no apparent change in the muscle wasting and weakness. The disease process was still limited to the quadriceps in the lower limbs and the deltoid and triceps muscles in the upper limbs, although there was moderate weakness of the trunk; no skin lesions were present.

FIG. 2.—Case 2: showing the wasting of the quadriceps and position of muscle biopsy.

Re-testing the muscles electrically, it was found that

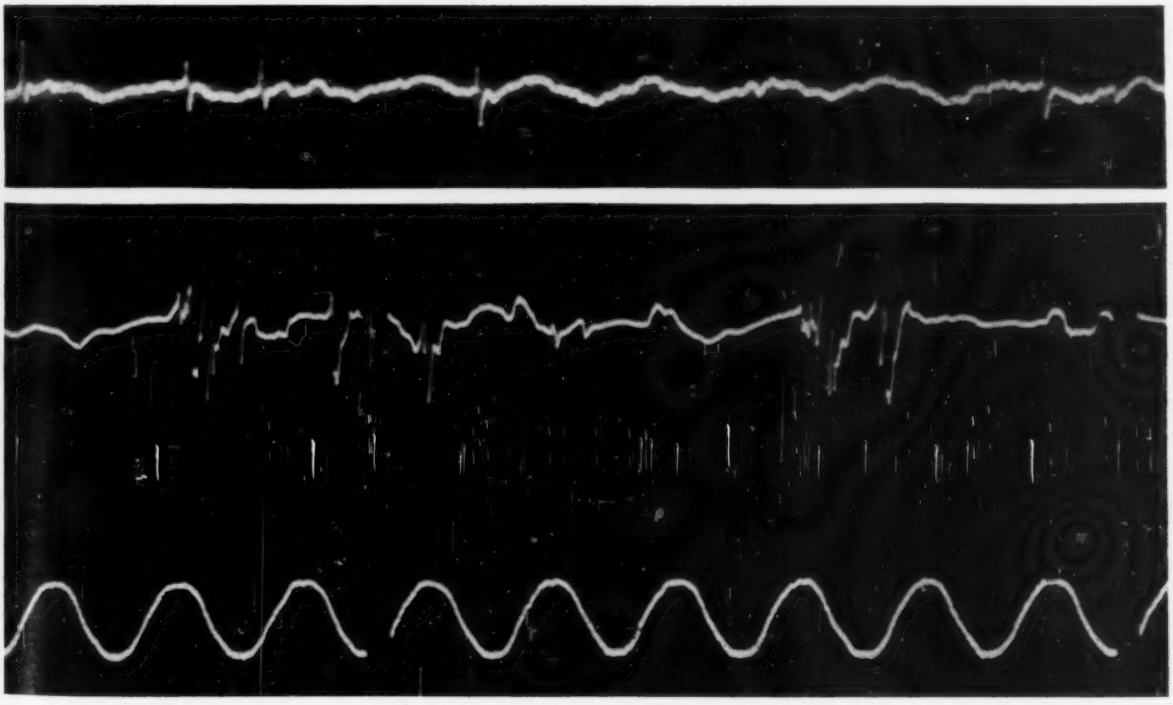

FIG. 3.—Electromyogram of quadriceps of Case 2. Calibration 50 cycles at 500 microvolts. Top tracing shows spontaneous fibrillation potentials. Second tracing shows disintegrated motor action potentials with reduced activity on full volition.

the intensity duration curves of both quadriceps and triceps muscles were normal. The left quadriceps (vastus medialis) showed discrete high-voltage long-duration polyphasic potentials. The right deltoid showed an atypical myopathic pattern.

Case 2.—Mrs. D. H., aged 52, was admitted on September 5, 1958, complaining of weakness of the legs. In November, 1957, she had a mild attack of influenza from which she made a complete recovery. In January, 1958, she noted difficulty in getting out of a chair and in walking upstairs and in April, 1958, when she consulted her doctor, he found wasting of the thigh muscles. She did not think that the wasting or weakness was increasing and she could play a round of golf without difficulty. There was no pain or sensory symptoms. There was nothing relevant in the past history and no family history of weakness of the limbs.

On examination there was considerable wasting of both quadriceps (Fig. 2), especially in the distal halves of the muscles; no fasciculation was seen. There was marked weakness of both quadriceps but no other wasting or definite muscle weakness was found. The knee jerks were absent, the other reflexes were normal, and there was no sensory impairment. The urinary creatinine level was 2·7 g. in 24 hours, creatine 0·1 g. in 24 hours, serum proteins 7·1 g. per 100 ml. (albumin 4·7 g. and globulin 2·4 g. per 100 ml.), and the E.S.R. 25 mm. in one hour. Strength duration curves showed no significant abnormality in any part of either quadriceps.

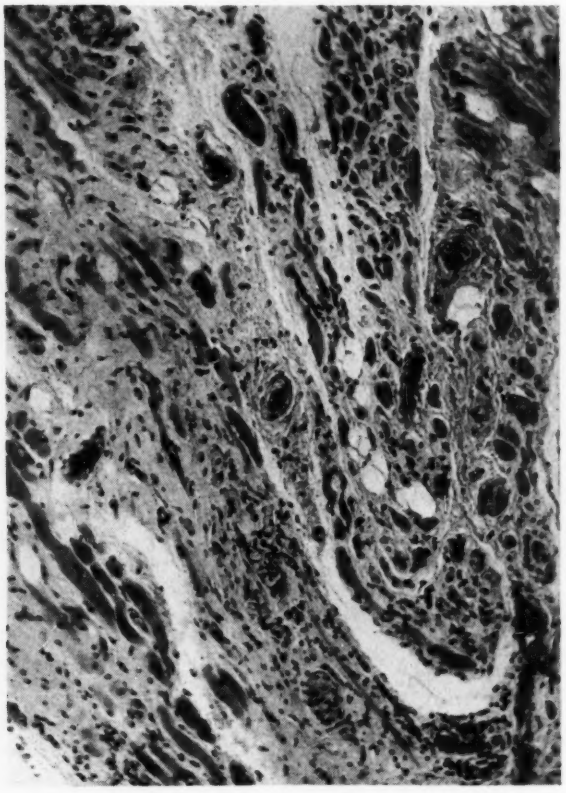

FIG. 4.—Case 2: Biopsy of vastus internus. ×75.

An E.M.G. was normal on two occasions while she was in hospital but was repeated on November 19, 1959, by Dr. J. T. Richardson. A small patch of fibrillation, together with a myopathic pattern, was found in the left quadriceps muscle (Fig. 3). Intensity duration curves of both quadriceps were normal. A biopsy of the right vastus medialis (Fig. 4) showed a very severe loss of muscle fibres with extensive fibrosis and adipose tissue replacement. A small number of fibres of approximately normal size were seen but no enlarged fibres, and the majority were in all stages of vacuolation and degeneration. Muscle spindles stood out clearly and generally appeared normal although occasional spindles also showed degeneration. Some clumps of sarcolemmal nuclei were seen but there was, on the whole, little evidence of regeneration. Nerve bundles, as stained by Holmes' method, showed a normal appearance with no empty Schwann tubes apparent. Inflammatory cells were numerous and fairly evenly scattered but occasionally they accumulated around blood vessels. Neutrophils were scanty, most of the inflammatory cells being lymphocytes and plasma cells and a few resembled mast cells. There was no sign of arteritis, fungi, or other infective agent, and no sign of sarcoidosis.

The patient was seen again in November, 1959, and there had been no change in her condition except that the quadriceps were slightly weaker. In view of the relative lack of disability and possible side-effects from the treatment, it was not considered advisable to give her steroid drugs.

Discussion

In 1923, Bramwell recorded two middle-aged men with wasting and weakness limited to the quadriceps of both legs, in one the vasti interni were especially involved and in the other the lower two-thirds of the thighs. The weakness had come on gradually, in the first over the course of a year, and in the other over six to seven years. There was no other wasting or weakness and the knee jerks were absent while the other reflexes were normal. Electrical testing showed a quantitative reduction of response in the wasted part of the quadriceps and Bramwell considered that these patients were examples of a myopathy limited to the quadriceps. In 1939, Denny-Brown, at a clinical meeting, showed the first case recorded in this paper. In the subsequent discussion, Symonds said that there were patients in whom wasting and weakness of the quadriceps, however long the condition persisted, might remain confined to those muscles. In 1956, Walton described two men, one aged 22 and the other 57, with wasting and weakness of the vasti interni and enlargement of the vasti externi, and biopsy in the younger patient showed the typical appearance of a muscular dystrophy. The second patient refused a

biopsy. The younger patient was followed up for four years from the onset and the older one for four years after being first seen (in all, nine years from the onset of symptoms) and their condition had not deteriorated during this period.

In our first patient, over the 20 years since the case was described by Denny-Brown, there has been only very slow deterioration. There has been some spread of the muscle weakness in the 14 years after the quadriceps weakness was first noticed; she complained of some weakness of the arms and this was found to be due to wasting and weakness of the triceps with absent triceps jerks and, at about the same time, she developed slight weakness of the flexors and extensors of both hips and slight weakness of the lower trunk muscles, but over the last nine years the weakness has increased only very slightly.

Difficulties arise in the nosological classification of these cases. They are undoubtedly myopathic in the sense that the condition is primarily muscular rather than neurogenic but the problem remains whether they should be considered as muscular dystrophies or as examples of polymyositis. When Denny-Brown reported our first case in 1939 he considered that the pathological changes on muscle biopsy were the same as in the two women recorded by Nevin in 1936 in whom there was considerably more widespread muscle involvement, starting in one at the age of 59 and in the other at the age of 57. Nevin considered that the pathological changes were different from those usually seen in muscular dystrophy in that degeneration of muscle fibres had occurred not by gradual atrophy but by intense degeneration in which muscle fibres had broken down, the sarcolemmal sheaths had disappeared, and the debris of degenerating muscle and proliferated sarcolemmal nuclei had called forth an apparently phagocytic response. He considered the possibility of polymyositis but thought this improbable on clinical rather than pathological grounds, the long history with good general health, the complete absence of contractures and the absence of involvement of the skin being unlikely in polymyositis. He finally regarded his cases as examples of progressive muscular dystrophy but pathologically distinct from other late cases recorded in the literature. In 1951, Shy and McEachern described 12 patients, 11 women and one man, with clinical and muscle biopsy features similar to those of Nevin's two cases and suggested the name of menopausal muscular dystrophy for the condition. The authors also showed that in some of these patients improvement occurred with administration of wheat germ oil or cortisone. Adams, Denny-Brown, and Pearson (1953) consider that these patients are in fact suffering from chronic polymyositis rather than a muscular dystrophy and Walton and Adams (1958) are of the same opinion. No muscle biopsy of the muscles mainly affected in our first case has been done since 1939; in the second case the findings were of a similar type to those in the first case in 1939 with, however, a definite inflammatory reaction. We consider that these two patients are suffering from chronic polymyositis rather than a progressive muscular dystrophy.

The biopsy findings show the two common types of abnormality seen in polymyositis. In Case 1 there was focal necrosis of muscle fibres with secondary phagocytic changes and in Case 2 inflammatory cells were seen between the muscle fibres. A rash is by no means always a feature of polymyositis, and fever, leucocytosis, and other evidence of inflammation are often lacking.

In the first patient, electro-myography gave a record indistinguishable from a muscular dystrophy, but in the second patient earlier records were normal but later ones gave a myopathic pattern with, in addition, fibrillation which is not found in muscular dystrophy.

Summary

A patient, reported in 1939, with wasting and weakness of the quadriceps, has been followed up for 20 years, in which time there has been very slow spread of the muscle involvement.

A second patient with similar localized wasting and weakness of the quadriceps and marked changes on muscle biopsy is reported.

It seems probably that these patients are suffering from chronic polymyositis rather than from progressive muscular dystrophy.

Muscle biopsy may be necessary to determine the cause of wasting of the quadriceps muscles.

We would like to thank Dr. A. T. Richardson and Dr. Euan Campbell, of the Royal Free Hospital, for their help with the electromyograms.

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ORIGIN OF ECHOES IN THE ECHOENCEPHALOGRAM

BY

BRITA LITHANDER

From the Paediatric Clinic, Karolinska Sjukhuset and the Neurological Clinic, Södersjukhuset, Stockholm, Sweden

Echoencephalography was described in 1956 by Leksell, who showed that the ultrasonic echo 'could be used for practical diagnostic purposes through the intact skull'. According to Leksell, when recording at the temporal region with the probe directed toward the corresponding region on the opposite side of the skull, an echo regularly appears which derives from the midline structure of the brain. Leksell's method has proved very useful, since it is quick, simple, and relatively reliable. In addition to the midline echo, Leksell observed a number of other echoes, 'which appear to come from the boundaries between brain tissue and cerebrospinal fluid'.

In a later publication, Leksell (1958) expressed the opinion that the pineal body is the prime source of the midline echo. Vlieger and Ridder (1959) found that the midline echo originates in the longitudinal fissure, not in the falx cerebri. They also recorded echoes which they believed derived from the ventricles. Gordon (1959) expressed the opinion that the midline echo originates primarily in the septum pellucidum and also in the third ventricle, and that these echoes are often indistinguishable.

The investigations made hitherto have not provided a satisfactory answer to the question whether one or more structures yield the midline echo. Nor has the origin of the lateral echoes been fully clarified, and further study is required to elucidate this problem.

The purpose of the present study is to try to determine from what structures in the brain the midline echo and the lateral echo derive.

To locate the structures from which echoes originate, I have developed a method using hypodermic needles as indicators, and a water tank method has been evolved in order to localize these structures with greater precision.

Physical Principles

Ultrasound is produced when short pulses of high-frequency electrical energy are applied by a transmitter to a piezoelectric crystal which produces the mechanical vibrations. Ultrasound is propagated at different velocities in different media. An interface between two media with different velocities of propagation of ultrasound reflects part of the ultrasound back to the crystal where it is retransformed to electric energy. Air is a poor medium for propagation of ultrasound with the ultrasound frequencies used in this investigation, practically all the ultrasound being reflected by an interface of air.

The reflection of ultrasound in general follows the laws of optics. Consequently, if the ultrasound meets an interface between two media at right angles, some of the sound passes through and some will be reflected back to the crystal; with a convex surface the reflected beam will diverge, and with a concave surface it will converge.

In water the ultrasound at first is propagated without diverging over a distance which varies with the frequency and with the diameter of the probe. Thereafter, the sound beam diverges with a specific angle of deviation. With a 2 Mc./sec. 10 mm. probe, the length of the parallel beam is 34 mm., and with a 2 Mc./sec. 24 mm. probe it is 215 mm.

Apparatus

The standard ultrasonic echo apparatus (Krautkrämer model USIP 9) was used with an adapted Polaroid-Land camera (Leksell, 1958).

The following types of barium titanate probes were used: 2 Mc./sec. 24 mm. diameter for examinations through the intact skull in adults; 2 Mc./sec. 10 mm. diameter for direct application on the brain in adults; 4 Mc./sec. 10 mm. diameter or 2 Mc./sec. 10 mm. for examinations in infants. Liquid paraffin was used as a coupling medium between probe and skull.

Method I

Determination of Extent of Midline Echoes in Infants.—In adults the midline echo can usually be recorded only in a small area in the temporal region. This may be because the echo-producing midline structure has such a limited extent in the sagittal plane of the skull that it can only be recorded at right angles to the sagittal plane from a very small area. It may also be due to the fact that the skull is thinner or less dense here and that ultrasound therefore passes through more easily. A study of the midline echo in infants, whose entire skull is thin, was therefore considered useful.

The investigation was made on nine healthy newborn infants and two infants who had died from asphyxia at

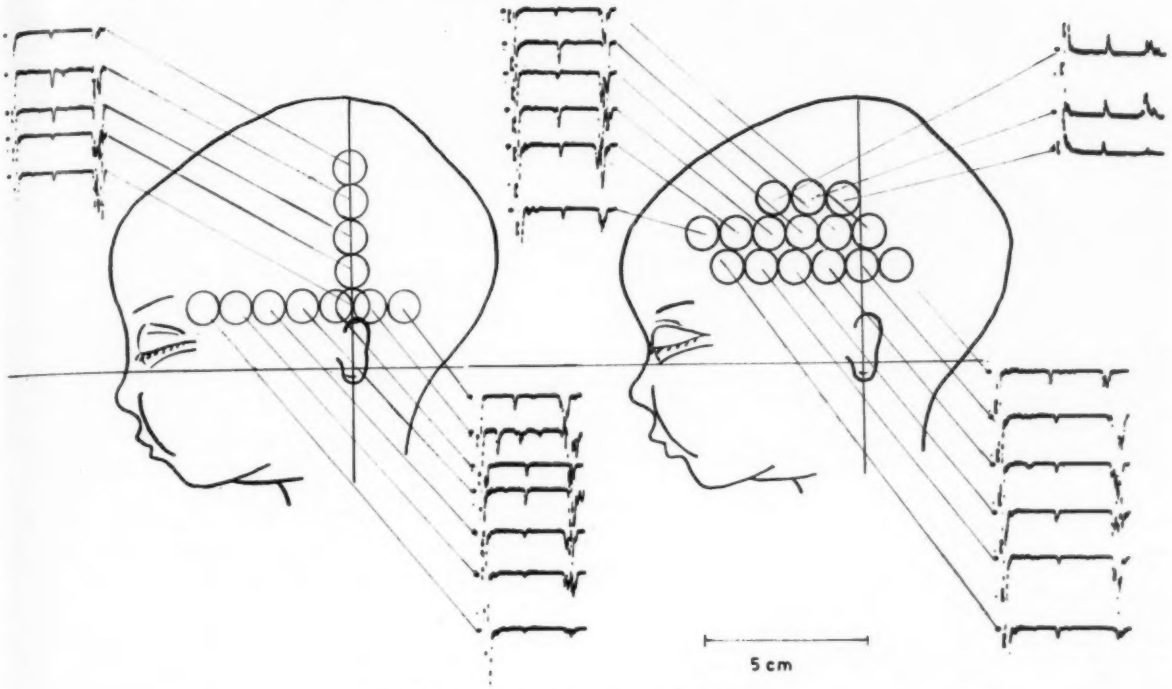

FIG. 1.—Extent of midline echoes in infants.

birth. No difference in the echoencephalograms was found between the living and the dead infants.

To secure corresponding measuring points from case to case, I used a system of coordinates; the abscissa is formed by an imaginary baseline through the external auditory meatus and the lower edge of the orbit; the ordinate is a line through the external auditory meatus at an angle of 90° to the baseline, the aural ordinate.

Results

With the probe (2 Mc./sec. 10 mm.) placed 1 cm. above the baseline and applied at right angles to the mid-sagittal plane, a distinct midline echo was recorded along a horizontal line extending approximately 4 to 5 cm. in front of and 1 to 2 cm. behind the aural ordinate. The midline echo was also recorded to about the same extent along a line 2 or 3 cm. above the baseline. Recording along the aural ordinate gave a distinct midline echo for a distance of 4 to 5 cm. (Fig. 1). The midline echo in infants could thus be recorded over large areas of the frontal, temporal, and parietal regions, *i.e.*, within the entire area in which the probe could be applied almost at right angles to the sagittal plane of the skull.

In children whose skulls are flattened laterally this area is larger than in those with more spherical heads. Under favourable conditions, the midline echo can thus be recorded over a relatively large area. This indicates that the midline echo in children is not solely produced by a small structure like the pineal body. It might be concluded from these observations that probably the most important cause of the limitation of the area from which the midline echo derives in adults is the density which characterizes the adult skull, with the exception of the relatively thin temporal bone.

Method IIA

Location of Echo-producing Structures with Hypodermic Needles.—The roof of the skull of a cadaver is sawed off and carefully removed. To prevent leakage of the cerebrospinal fluid it is important not to damage the cerebral meninges.

Echoencephalography is done before and after removal of the roof of the skull to check that air has not entered the blood vessels and cavities of the brain and thus produced echoes not normally recorded *in vivo*.

A 2 Mc./sec. 10 mm. probe can be used when recording directly on the brain. This is of great advantage because this probe gives a narrower beam and has a greater resolving power than the larger 2 Mc./sec. 24 mm. probe. Furthermore, the initial pulse is shorter and thus scarcely encroaches on the echoencephalogram.

The probe is placed on the temporal lobe of the brain, a midline echo is sought and the probe is adjusted accordingly.

A needle inserted into the brain at right angles to the ultrasonic beam gives a strong echo, and this fact can be utilized in locating an echo-producing structure. A long needle is inserted in the brain and is moved until its echo coincides with the echo to be analysed. The needle is inserted to a depth at which its echo is barely visible on

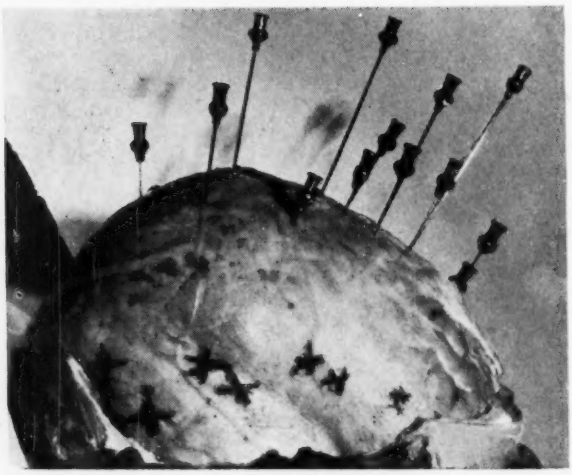

FIG. 2.—Brain with needle indicators inserted. Crosses show positions of the probe at the various recordings.

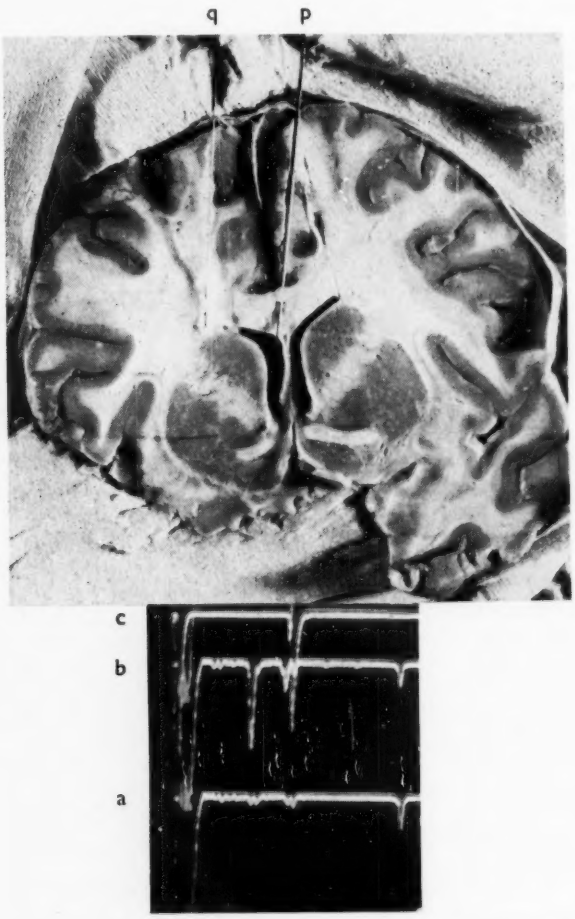

FIG. 3.—Method IIA. Section of brain with points of needles near the left lateral ventricle and close to the septum pellucidum. Recording from the left side directly on the brain: a, echoencephalogram before insertion of needles; b, echoencephalogram after insertion of needles p and q; c, control.

the echoencephalogram, and is then left in that position (Fig. 2). Formalin is then injected into the carotid arteries and the brain is removed and sectioned. The location of the needle can now be determined and conclusions can be drawn concerning the structure from which the echo emanates.

Results

Seven cases were studied with method IIA and 59 echoes were analysed. In order to illustrate the results of the investigations many figures have been included, and have been selected with the object of illustrating the different structures from which an echo can be recorded. The same structures have yielded echoes in different patients, with the exception that in some instances it has not been possible with certainty to relate the echo to a definite anatomical structure.

Record a in Fig. 3 shows the appearance of the echoencephalogram before needles were inserted into the brain. We see the initial echo at the extreme left; at the extreme right is the bottom echo from the opposite surface of the brain. Between these two echoes, two double echoes are recorded; the one on the right is the midline record b, and was made when two needles were moved until their respective echoes coincided precisely on the echoencephalogram with the first spike in each double echo. Record c is the 'control deflection', which indicates the sagittal midplane (Lithander, 1960). This is the same as the transmission pulse described by Vlieger and Ridder (1959). This method of ascertaining the exact midpoint has also been used by Jeppson (1960).

We see in the picture that the left needle appears to point to the left ventricle, although the latter was accidentally cut somewhat obliquely. The right needle points to the left side of the septum pellucidum. The second spike in the right double echo therefore presumably represents the right side of the septum pellucidum. This is in agreement with the location of the control echo between these echoes, which derive from the left and right side of the septum pellucidum.

Fig. 4 shows, likewise, the position of the needles in the Sylvian fissure and in the third ventricle. Fig. 5 illustrates how the echoes in record a are identified by the needles. The right needle is inserted behind the others and can be seen protruding from the brain. Its point is, however, in the bottom of the lateral ventricle at the boundary between brain and cerebrospinal fluid. The next two needles appear to be situated on the boundary between gray and white substance. The last needle is in the Sylvian fissure. Fig. 6 shows echoes which originate from the lateral ventricle and the longitudinal fissure or from the falx.

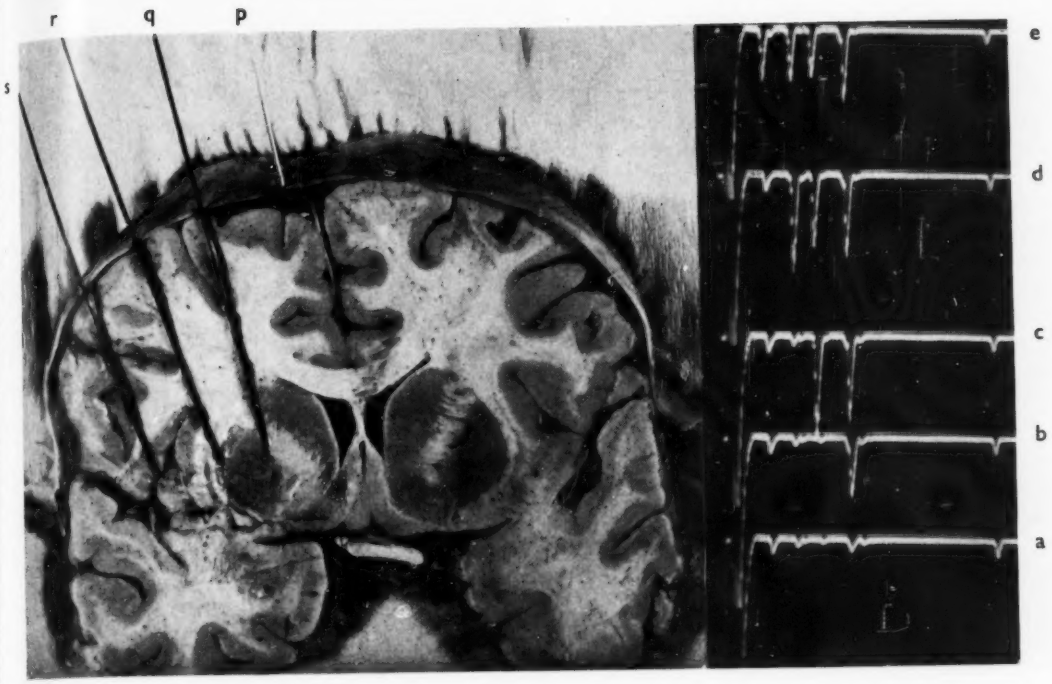

FIG. 5.—Method IIA. Section of brain with points of needles in the Sylvian fissure in the boundary between white and gray matter and in the left ventricle. Recording from the left side: a, before insertion of needles; b, after insertion of needle p; c, after insertion of needles p, q; d, after insertion of needles p, q, r; e, after insertion of needles p, q, r, s.

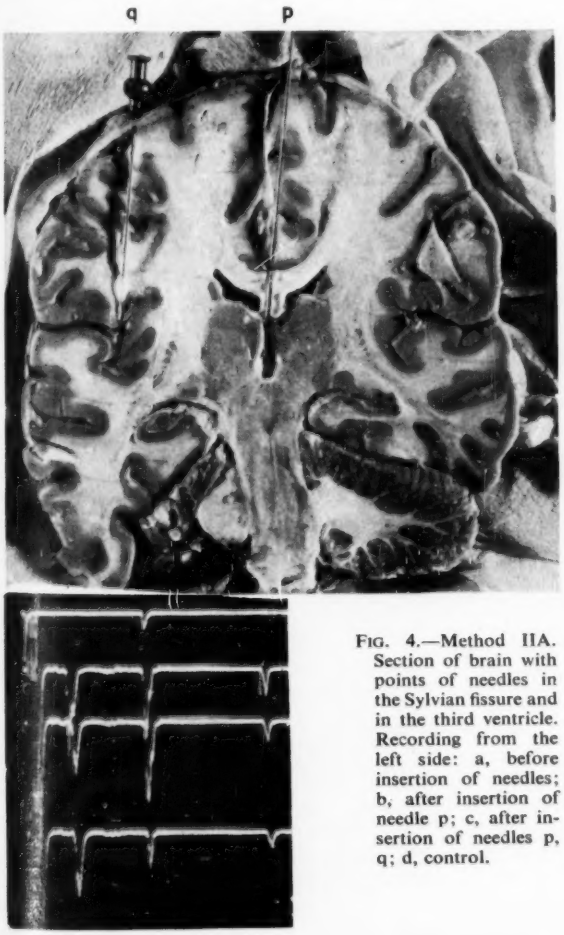

FIG. 4.—Method IIA. Section of brain with points of needles in the Sylvian fissure and in the third ventricle. Recording from the left side: a, before insertion of needles; b, after insertion of needle p; c, after insertion of needles p, q; d, control.

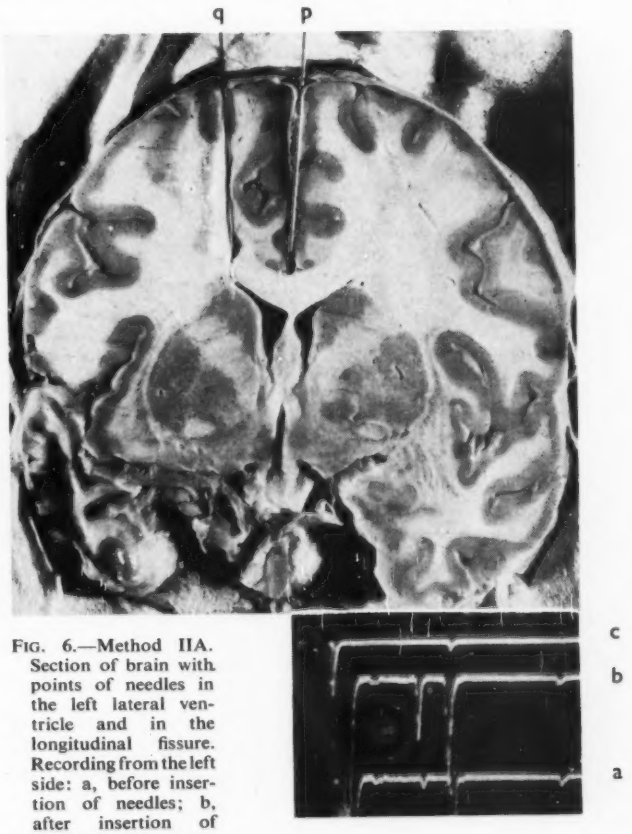

FIG. 6.—Method IIA. Section of brain with points of needles in the left lateral ventricle and in the longitudinal fissure. Recording from the left side: a, before insertion of needles; b, after insertion of needles p, q; c, control.

With this method, the sagittal plane in which the echo-reflecting structure is situated can be determined. Owing to the width of the ultrasonic beam, however, it is not possible to determine exactly in which horizontal or frontal plane this structure is located. But in the present investigation, the position of the point of the needle corresponds to the upper limit of the beam. The structure from which the echo derives is thus to be found in the same horizontal plane as the point of the needle or below it.

In many cases, however, there is no difficulty in determining the structure from which a specific echo derives. In Fig. 3, for example, the right needle points to the septum pellucidum, and there is scarcely any doubt that the midline echo derives from the septum pellucidum. The left needle, on the other hand, is not in exactly the same frontal plane as the horn of the lateral ventricle. A comparison with the right lateral ventricle shows that the position of the point of the needle in the sagittal plane corresponds to the lateral horn of the left lateral ventricle.

Using this method, we thus find that the midline echo derives from a number of different structures in the midline. The lateral echoes come from the boundary between brain substance and cerebrospinal fluid (ventricles and gyri) and between gray and white substance (thalamus, internal capsule, and external capsule).

It should be borne in mind, however, that conditions are more favourable when examinations are made on the brain itself than through the intact skull, and that more echoes can be recorded than when the ultrasound has to pass through the skull.

Method IIB

Method II was again used but a probe was placed on the skull instead of directly on the brain in order to make the experimental conditions resemble a routine clinical examination as closely as possible. A strip of bone measuring approximately 1 to 2 × 10 cm. is sawed out of the roof of the skull and a probe (2 Mc./sec. 24 mm.) is placed on different points over the temporal region. The midline echo is sought at these points, and a needle is inserted into the brain through the opening in the skull. As in the foregoing investigation, the needle echo is made to coincide with the echo to be analysed. Formalin is then injected into the carotids and the brain is removed and sectioned.

Results

Fig. 7 shows the needle in the septum pellucidum. In this case it is impossible to determine whether the midline echo derives from the third ventricle or the septum pellucidum.

From Fig. 8 it is evident that the needle penetrates the midplane of the pineal body down toward the aqueduct. Considering that the point of the needle is situated in the upper horizontal plane of the ultrasonic beam, the echo presumably derives from the aqueduct.

Fig. 9 shows a double midline echo and the needle (in this special case inserted slightly too deep) indicates that the echo derives from the third ventricle.

Fig. 10 shows a lateral echo produced by the lateral wall of the posterior horn. The midline echo appears to be derived either from the longitudinal fissure or the falx. The boundary surfaces between the longitudinal fissure and the falx are so close to one another that it is impossible to determine with a needle in which of the two an echo arises. If the falx was touched with the needle, the echo changed its appearance, which was not the case if the inner surfaces of the hemispheres were touched.

Fig. 11 illustrates an attempt to determine if it is really the falx that yields the midline echo. In this experiment, the falx was cut in two rostrally to the probe through the opening in the roof of the skull. When this was done, the midline echo disappeared, but it recurred every time the falx was stretched (Fig. 11a, b, c).

No midline echo could be recorded if the falx was removed by drawing it occipitally to the probe (Fig. 11d). It reappeared when the falx was again drawn forward in a rostral direction and stretched (Fig. 11e). The falx thus yields a distinct echo.

This investigation with the probe placed on the outer surface of the skull reveals, like recordings directly on the brain, that the midline echo arises from different structures in the midline and that the interface between brain tissue and cerebrospinal fluid yields an echo. The width of the ultrasonic beam makes it difficult to determine whether the echo from the boundary between gray and white substance is recorded on the skull; however, a number of recordings indicated that this is the case.

With this method, it is possible to determine the location of the echo-producing structure in the sagittal plane only. Sometimes this is sufficient to identify a specific echo, but sometimes one may also need to determine in which horizontal and vertical plane the echo arises, and the investigations were therefore continued with another method to meet this situation.

Method III

Echoencephalography with Brains Immersed in a Water-tank.—A probe (2 Mc./sec. 24 mm.) is applied to the outside of a plastic tank filled with degassed water in such a way that half the surface of the probe is above the level of the water. A bottom segment of the surface of the probe is screened off with a double layer of plastic

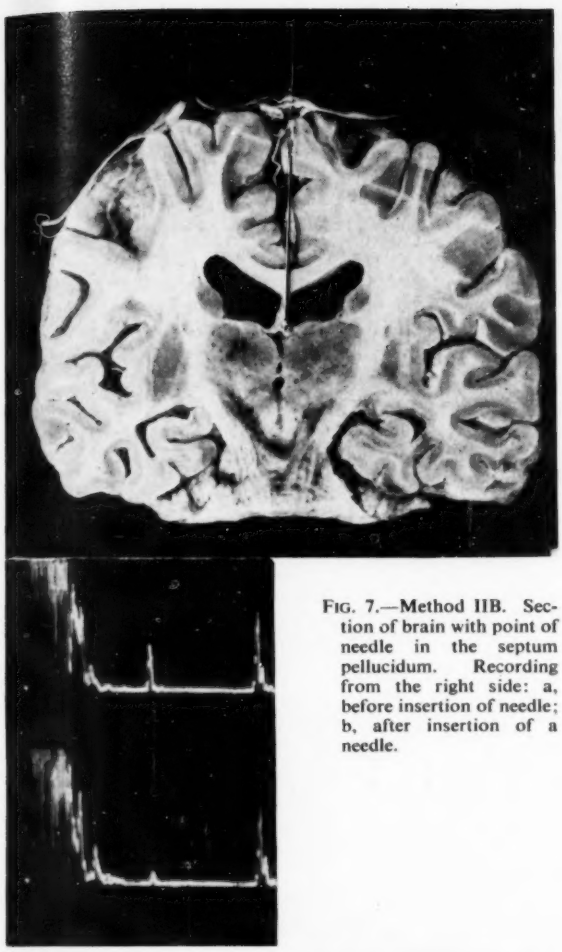

FIG. 7.—Method IIB. Section of brain with point of needle in the septum pellucidum. Recording from the right side: a, before insertion of needle; b, after insertion of a needle.

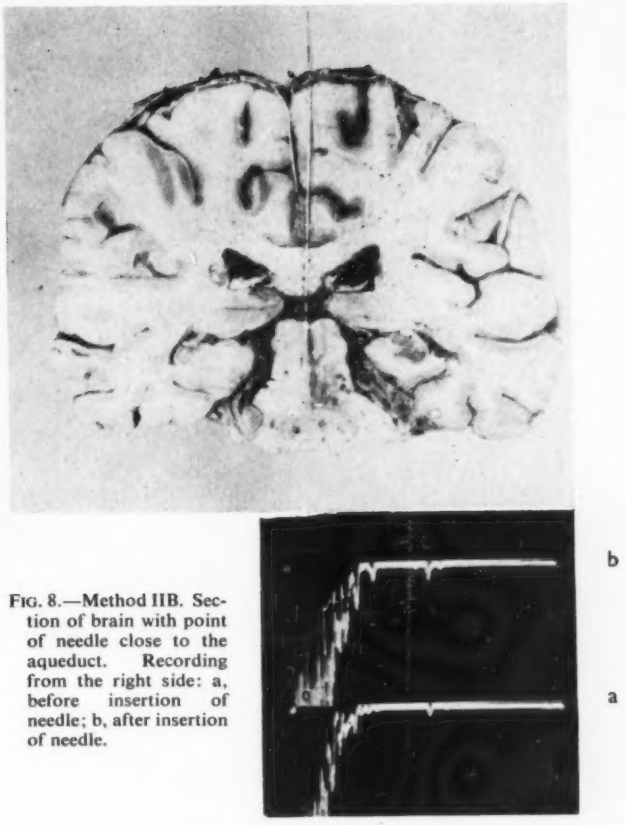

FIG. 8.—Method IIB. Section of brain with point of needle close to the aqueduct. Recording from the right side: a, before insertion of needle; b, after insertion of needle.

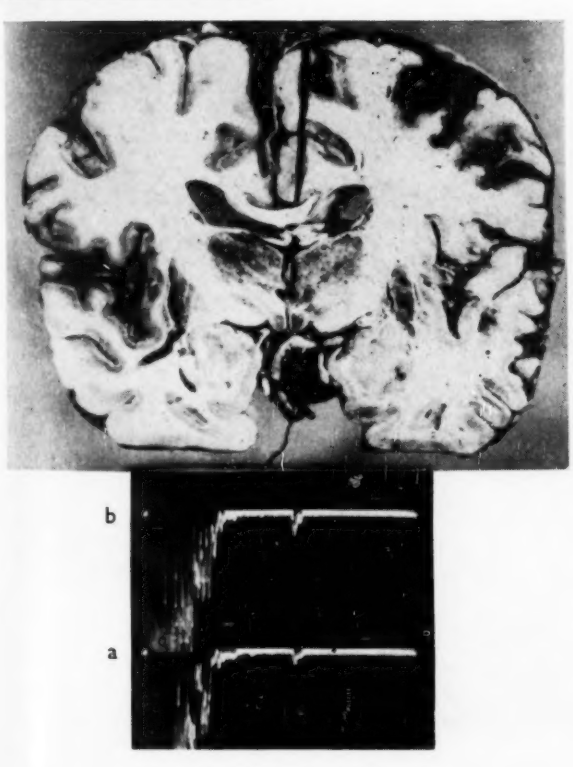

FIG. 9.—Method IIB. Section of brain with point of needle in the third ventricle: a, before insertion of needle; b, after insertion of needle.

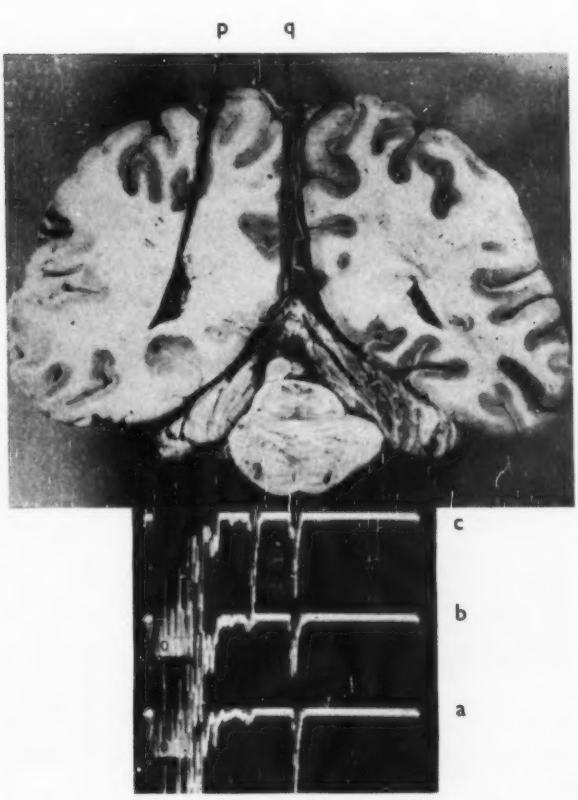

FIG. 10.—Method IIB. Section of brain with points of needles in the longitudinal fissure and in the left posterior horn. Recording from the left side: a, before insertion of needles; b, after insertion of needle p; c, after insertion of needles p, q.

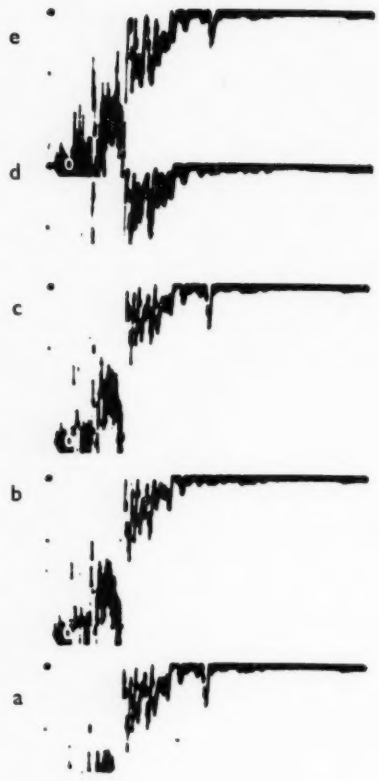

FIG. 11.—Echoes from falx under varying experimental conditions: a, echoencephalogram under normal conditions; b, after sectioning of falx; c, after stretching of falx; d, after removing falx; e, after replacing and stretching falx.

foil with cellulose wadding between to trap air. In this way the probe is screened off with air so as to give a thin, slit-like beam of parallel ultrasonic rays along and immediately beneath the surface of the water.

Determination of the Horizontal Plane.—A brain is placed in a skull in order to reproduce as closely as possible the damping and refracting conditions of an investigation on the skull. The brain in the skull is placed in the water tank, and by moving the skull vertically the ultrasound can be made to pass into the brain in a clearly definable horizontal plane. Unprepared brains as well as brains fixed in formalin were used in the experiments. After it was found that the echoes arose in the same structures in both cases, brains fixed in formalin were commonly used for the sake of convenience.

Determination of the Frontal Plane.—The brain is sectioned coronally and placed in the skull. The skull is then immersed in the water-tank and moved in a sagittal direction until the beam just strikes the cut surface.

In this way the echo-producing structures on the cut surface of the brain can be determined. In doubtful cases and in order to check the dimensions of the ultrasonic beam, the needle is applied along the cut surface next to the structure whose echo is to be analysed. The structure suspected to be the origin of the echo can also be displaced to facilitate identification of the echo-producing structures. By cutting off pieces of the brain successively, a complete echoencephalographic chart of the brain can be made.

Results

Fig. 12 illustrates two echoencephalograms recorded at two different levels on the same section of brain. The echoes in record a were recorded from the Sylvian fissure, the thalamus and the third

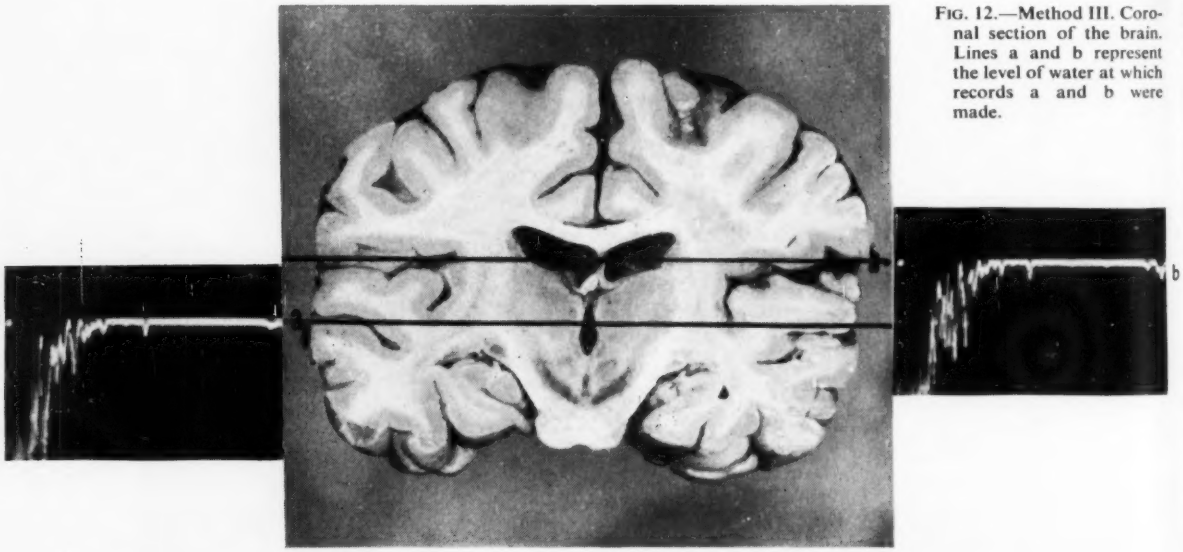

FIG. 12.—Method III. Coronal section of the brain. Lines a and b represent the level of water at which records a and b were made.

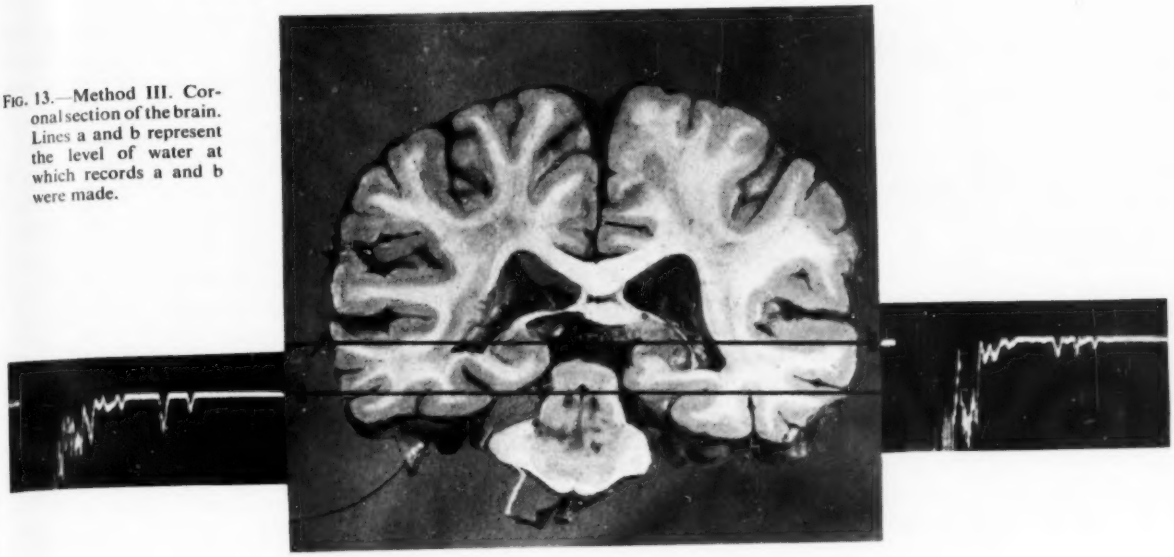

FIG. 13.—Method III. Coronal section of the brain. Lines a and b represent the level of water at which records a and b were made.

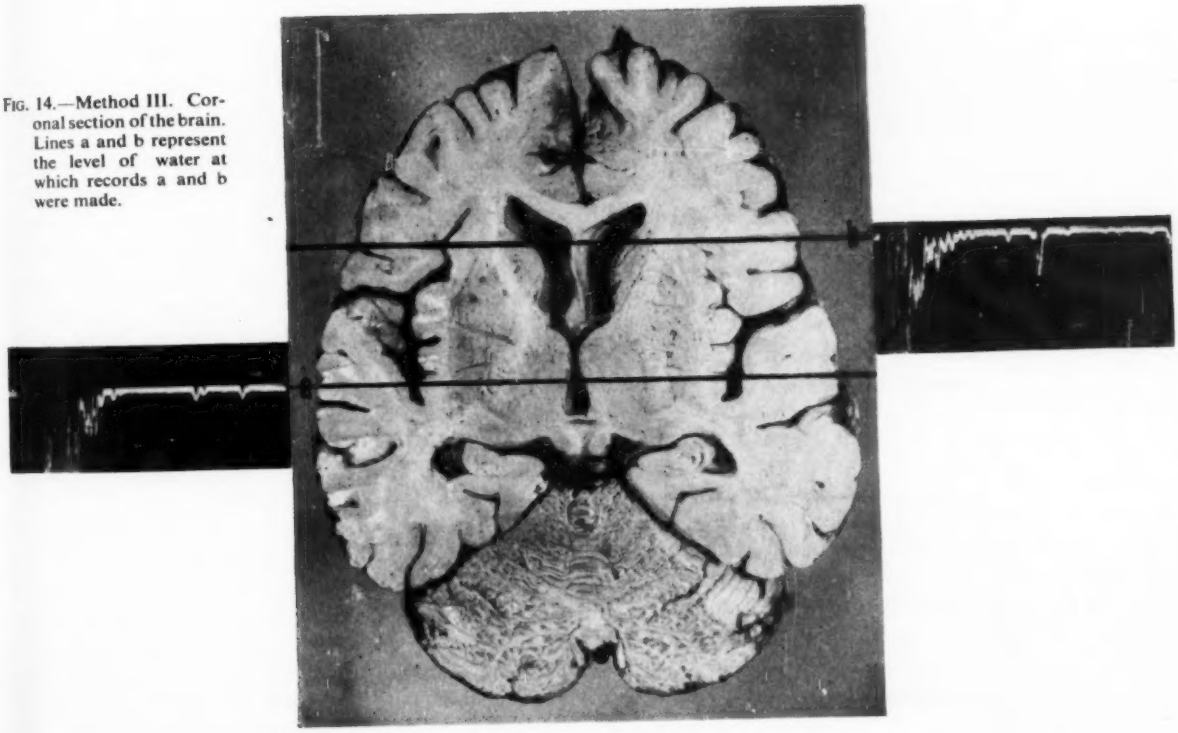

FIG. 14.—Method III. Coronal section of the brain. Lines a and b represent the level of water at which records a and b were made.

ventricle, in record b from the Sylvian fissure, the lateral ventricle, and the septum pellucidum.

Fig. 13 illustrates two echoencephalograms recorded from a section of brain removed further occipitally. Record a has two distinct echoes in its central part; the left comes from the left lateral margin of the pons, while the right comes from the aqueduct.

In record b, recorded in a somewhat higher horizontal plane, the echoes in the middle arise in the left margin of the transverse fissure, in the pineal body, and in the right margin of the transverse fissure.

Fig. 14 illustrates two echoencephalograms from a brain cut horizontally. The double midline echo in record a originates in the third ventricle and the

FIG. 15.—Echoencephalographic investigation of the pineal body through skull of normal thickness: a, record with pineal body removed; b, pineal body removed and point of needle shows its site; c, uncalcified pineal body in place; d, calcified pineal body in place.

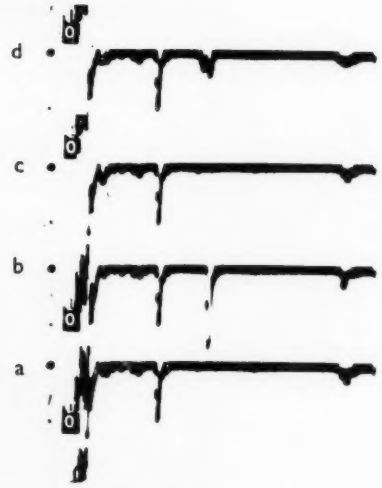

FIG. 16.—Echoencephalographic investigation of the pineal body through skull of exceptional thinness: a, pineal body removed; b, pineal body removed and point of needle shows its site; c, uncalcified pineal body in place; d, calcified pineal body in place.

midline echo in record b from the septum pellucidum.

Fig. 15 shows a special experiment with the pineal body.

A brain with a pineal body not visible on the radiograph was sectioned horizontally immediately above the pineal body. The pineal was dissected and then replaced. The lower half of the brain with the pineal body was placed in a skull of normal thickness and then immersed in a tank of water. The experiment was performed both with a screened probe and an unscreened probe.

Record a represents an echoencephalogram with the pineal body removed; no midline echo is seen. In record b a needle has been held with the point at the site of the pineal body to check that the ultrasonic beam actually passed through the place where the pineal body would normally have been. A strong midline echo was recorded. In record c the needle had been removed and the uncalcified pineal body replaced; no midline echo was recorded. In record d, the uncalcified pineal body had been replaced by one which was visible on the radiograph; no midline echo was recorded here either. Thus no midline echo could be recorded through the skull from either an uncalcified or a calcified pineal body. Nevertheless midline echoes could be recorded from, for example, the septum pellucidum and the third ventricle.

Since the thickness of the bone of the skull might conceivably be the reason that no echo was recorded from the pineal body, the experiment was repeated in the same way with the same brains and with the same pineal bodies, but with an exceptionally thin skull. Record a in Fig. 16 shows an echoencephalogram with the pineal body removed; no midline echo is seen. In record b a needle echo was recorded from the former site of the pineal body. Record c shows an echoencephalogram with an uncalcified pineal body in place; no midline echo was recorded. In record d a double midline echo was recorded from a calcified pineal body. Consequently an echo from a calcified pineal body can be recorded through the skull provided the bone is thin.

Using this water-tank method, the midline echo was recorded from the falx, the septum pellucidum, the third ventricle, the transverse fissure and the aqueduct, and from a calcified pineal body if the skull was thin.

Lateral echoes arise from ventricles and gyri and from the boundary between gray and white substance.

Discussion

The purpose of the investigation was primarily to determine which structures in the brain give echoes

recordable on the skull. With the exception of the experiments using method IIA, the recordings were made through the skull.

It appeared from all the experiments that the midline echo is recorded from different structures. Which structure gives an echo seems to depend primarily on the placing of the probe and to some extent also on the shape and thickness of the skull.

A summary of the results of the investigation indicates that midline echoes may be formed by the following structures: aqueduct, transverse fissure, pineal body, third ventricle, septum pellucidum, and falx cerebri.

According to Leksell, the midline echo is produced primarily by the pineal body, whether calcified or not. He bases this opinion on experiments on brains in a tank of water without having the ultrasound pass through the skull. But it is clear from my investigation that a pineal body which cannot be visualized radiologically gives no echo which can be recorded through the skull. On the other hand, a pineal body with visible calcification can be recorded on the echoencephalogram through the skull on the condition that the bone is relatively thin. If the skull is relatively thick or dense, the damping effect will be so great that the echo of the pineal body cannot be recorded even though other midline echoes can be recorded, *e.g.*, from the falx cerebri, the septum pellucidum, and the third ventricle. The fact that echoes can be recorded from these structures when the pineal body does not give an echo is probably due to their having plane surfaces which effectively reflect the ultrasound, whereas the pineal body is a round structure against whose surface the ultrasound is reflected in different directions.

According to Vlieger and Ridder, the longitudinal fissure, but not the falx, is the source of the midline echo. They base this view on their findings that 'on several occasions a double midline reflection was seen'. By placing a thin steel blade in the longitudinal fissure, Vlieger and Ridder found that 'the reflection of the steel blade appeared exactly between the double midline reflection'. It would appear that the probe used was a 1 Mc./sec. with a diameter of 34 mm. If so, the ultrasonic ray would be approximately 34 mm. in diameter, and it would then be impossible to specify which structures in the midline yielded the echo. Even if one makes the recording high on the aural vertical, one cannot be sure with this probe that the midline echo does not come from the third ventricle, for example. An echo from the third ventricle is usually recorded as a double echo of the type Vlieger and Ridder demonstrated to prove their claim. That a thin steel blade in the longitudinal fissure gives an echo recorded in the middle of the double echo does not prove that the double echo arises in the longitudinal fissure. On the other hand, their opinion that the falx cerebri does not yield a distinct echo is disproved by the present investigation.

With regard to the lateral echoes, earlier researchers have considered that the ventricular walls give echoes. This view is based on the location of the lateral echoes on the echoencephalogram, although no method of verifying it has been presented. With the methods described above, however, it was possible to prove that this view is correct. Furthermore, it was found that echoes originate in the gyri, particularly the Sylvian fissure.

The finding that the boundary between gray and white substance yields an echo is somewhat surprising and is of essential interest. From the boundary between the thalamus and the internal capsule echoes can be recorded, which may easily be confused with ventricular echoes.

Summary

It was found that midline echoes could be recorded in infants over a lateral area which is relatively much larger than in adults. This suggests that the midline echo is not only produced by so small a body as the pineal.

A method using needle indicators in order to determine which structures give echoes is described. These experiments were performed on cadavers, both directly on the brain and on the skull.

The location of the echoes can be determined with greater precision with a screened ultrasonic beam in a tank of water by successive removal of parts of the brain.

These investigations show that midline echoes can be recorded from the falx cerebri, the septum pellucidum, the third ventricle, the transverse fissure, the pineal body, and the aqueduct. Lateral echoes originate in a number of boundary surfaces between brain and cerebrospinal fluid (ventricles and gyri) and, under favourable conditions, can be recorded from the boundary between gray and white substance (thalamus, internal capsule, and external capsule).

I wish to thank Prof. L. Leksell and Dr. S. Jeppson, Lund, who have kindly instructed me in the use of the Krautkrämer's apparatus. I am also indebted to Mr. S. Dahn, Technical X-ray Centre, Stockholm, for valuable advice. This study has been supported in part by the Association for the Aid of Crippled Children, New York.

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CEREBRAL TRAUMA IN INFANCY AND INTELLECTUAL DEFECT

BY

R. C. OLDFIELD and MOYRA WILLIAMS*

From the Institute of Experimental Psychology, Oxford

Discussion of the functions of the prefrontal areas of the cerebral cortex has evoked a bewildering variety of observations and hypotheses. Among the more incisive of recent features has been the observation, repeated by other workers, of Hebb and Penfield (1940) that it is possible for an adult human being to be deprived of both of these areas and exhibit little or no intellectual loss, at least to the extent that such loss can at present be assessed by formal or clinical psychological tests. Indeed, in cases in which the prefrontal area is removed on one side at operation after a period in which cerebral function was disordered by some pathological condition, such as epilepsy, intellectual function may markedly improve (Krynauw, 1950; Cairns, 1951). Controversies have arisen between those, such as Hebb, who have been struck by the apparently negligible disturbance which may be occasioned by complete loss of these areas, and those, like Goldstein (1936, 1944) who, largely basing their conclusions on the study of cases in which the parts are present but damaged, diseased, or degenerated, emphasize that specific failings of intellectual processes can be demonstrated by an appropriate test. It seems likely that some at least of these differences of opinion might be resolved if more were known of the difference between absence and disordered function of brain tissue and the effect on intellectual processes. The central nervous system affords little warrant for the idea that disease is equivalent simply to partial extirpation so far as disturbance of function is concerned. Goldstein contends that an important function of the prefrontal areas is the maintenance of varied systems of categories of thought and of abstract as opposed to concrete attitudes in high-grade behaviour. He supports this view, in fact, by reference to cases where tissue is present but damaged. Hebb, in criticizing him, tends to rely on showing that Goldstein's tests do not reveal these functional defects in cases where the tissue in question has been removed at operation.

A second interesting and related topic for speculation centres around the question whether cerebral, and in particular frontal, trauma sustained at an early age has the same later effects as those produced by damage in adult life. Ritchie Russell (1948) suggests, for instance, ". . . that by early or middle adult life the frontal lobes have already done much of their work by conditioning and moulding the pattern of the behaviour responses of the left parieto-temporal area. If this view is correct, injury to the prefrontal lobes in young children should lead to a very obvious failure of mental development, but it is difficult to get reliable information about cases of this kind". Of the two cases adduced by Russell, one is that reported by Norman (1945) in which very severe generalized mental defect followed an acute encephalopathic episode in a child, previously normal and healthy, at the age of 13 months. The patient died of pulmonary tuberculosis at the age of 19 years and necropsy revealed complete atrophy of both frontal lobes backwards to involve the lower part of the precentral gyri, leaving the upper part unaffected, and no cortical damage elsewhere. The other case cited by Russell is that further reported in the present paper.

Hebb (1942) is disinclined (*vide supra*) to accept the specific intellectual signs defined by Goldstein as inevitably consequent on severe frontal lobe damage. But he also seeks to distinguish between the outcome at the psychological level of a lesion sustained early and that of one suffered in adult life. This he proposes to do on the established basis that when a lesion occurs in adult life, abilities involving language, and in particular the capacity to define the meaning of words (vocabulary test), tend to be preserved provided no aphasia is present. The scoring on performance tests, on the other hand, is liable to be relatively depressed, to a greater or less extent. He is thus led to enquire whether the same differential tendency manifests itself in cases where the cerebral damage occurs in infancy. He has perforce to make use of "birth injury" case material to which certain obvious disadvantages attach, but is able to show that the characteristic pattern is one in which scores for verbal tests are not only not higher

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in relation to those for performance tests, but tend actually to be lower. He concludes that "the weight of evidence points to a more widespread and less selective effect of the large infant injury than of the adult injury". (It should be remarked that in this investigation Hebb is not primarily concerned with lesions confined to the frontal areas.) He goes on to remark that " . . . *more cerebral efficiency or more intellectual power is needed for intellectual development than for later functioning at the same level*" (his italics), a conclusion, if more general, not far removed from that of Ritchie Russell.

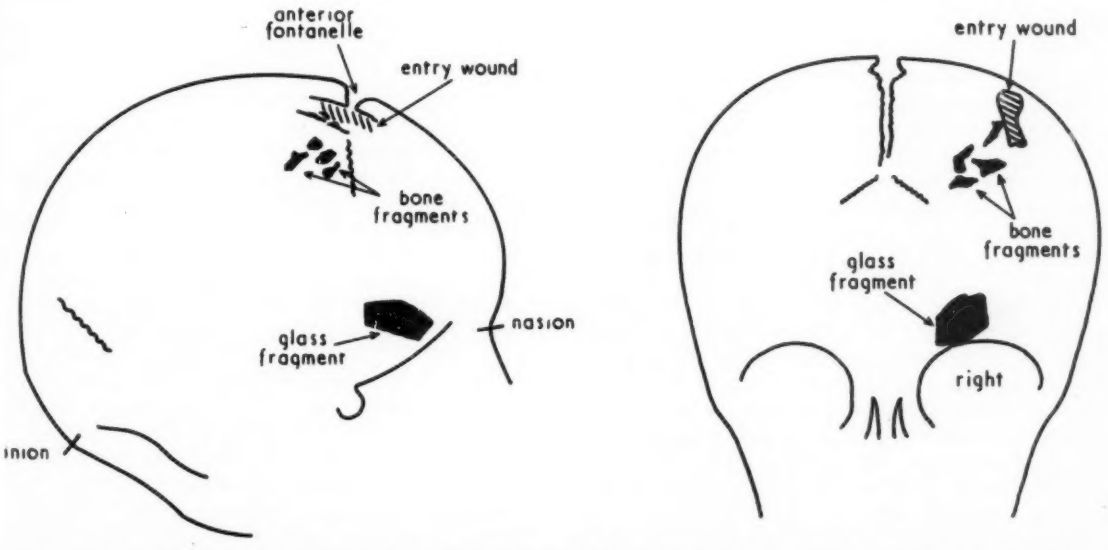
The difficulties involved in any conclusive test of such a hypothesis are numerous and manifest. Case material ("birth injuries" apart) which may throw light on the question is very scarce, and in no single instance likely to conform in all respects to what might be desired. In Norman's case, for instance, the lesion was bilateral, frontal, and virtually complete. Its extent and character and the structural normality of the rest of the cerebral cortex were established at necropsy. But the resultant dementia was so profound as to preclude any detailed qualitative study. The case described in the present paper, on the other hand, seems worthy of reporting because it lends itself to closer psychological assessment of the intellectual defect. But the absence of an air study (permission for which was refused) and of post-mortem findings make it impossible to be precise as to the extent of the lesion.

Case History

X, then aged 5½ months, was admitted to hospital in Liverpool on November 29, 1940, having sustained a penetrating head wound in an air raid. He had a lacerated scalp wound in the right parieto-frontal region with a piece of glass in the skull and was slightly shocked but apparently otherwise uninjured. At operation the following day the wound edges were excised, the glass removed from the skull and the wound sutured. No further exploration seems to have been made. Later that day the baby was described as being very pale but feeding well and not vomiting. At 10 p.m. the same evening both hands were twitching. Two days later tone and power of the limbs seemed normal, the pupils equal and reacting to light, knee jerks present and equal, and the general condition fairly good, but he was still very pale. His subsequent recovery seems to have been almost uneventful and at no time then, or subsequently up to the present day, were any neurological signs seen. On February 13, 1941, a purulent discharge from the right ear was noted, but this cleared up, and on March 4, 1941, he was said to be quite well. Radiographs (Figs. 1 and 2) revealed a foreign body (? glass) lying deep in the right frontal lobe. This is described later.

At a follow-up examination on July 31, 1941, when the child was 13 months old, no abnormality was detected, and his general development seemed to be that of a normal, healthy child. He was beginning to talk a little and trying to walk. He was said to be good tempered. At 21 months, on March 16, 1942, he was walking and talking and the matron in charge of the home in which he had been placed said he appeared perfectly normal to her. Towards the end of October in the same year, when he had been transferred to another home, he did not speak for a month, but was otherwise normal, though perhaps lacking in initiative. He understood and obeyed simple commands.

Up to the age of about 2 years, then, there was no direct evidence that the very severe injury to the right frontal lobe (with possible secondary involvement of the left) had exercised any effect upon this child's develop-



FIGS. 1 and 2.—Tracings of skull radiographs taken three days after the injury in 1940 when the patient was 5½ months old.

ment. His home circumstances would, however, have been a potential handicap to any child.

He was sixth in a family of eight, of which an elder brother was killed in the same air raid in which he was injured. The others are said to have made normal progress at school. The two younger children (2½ years old) talked to their parents but not to strangers. The family was of low economic status, living in "two rooms and a box" so dark that the gas had to be kept alight all day. The father, a pastrycook and confectioner, gave the impression from interviews and letters of being hysterical, aggressive, and of a litigious tendency. He was inclined to devote much of his attention to gaining as much as possible from the social welfare and other authorities out of his son's injury. Called up in 1942, he was medically discharged in 1943 suffering from "arthritis", a disease he seems to have contracted during his brief service with the forces. In March, 1943, the mother was provided with a certificate to the effect that she was suffering from neurasthenia and was unfit to be in sole charge of the boy. In consequence of this situation the child was placed in a series of homes. The father's account of his behaviour between 1943 and 1947 was one of steady deterioration. He was said to have been sent home from school by the medical officer because he hit small girls and tried to strangle the school cat. At home he made an unprovoked assault on his mother and younger sisters, causing the former to fall downstairs. He was frequently found eating food from dustbins, dog's food, and faeces. There is no direct check on these allegations, but in 1947 he was under psychiatric and neurological observation as a result of his father's persistent wish to get him committed to institutional care. In January, 1947, he was admitted to hospital in Liverpool for observation and treatment of sores on his toes, apparently caused by biting himself.

Admitted to Stoke Mandeville hospital in February, 1947 (aged 6½), nothing abnormal was detected on physical examination, but he was said to be uncooperative and easily distracted and it was on this account difficult to assess his intelligence. His behaviour in the ward was intractable and disturbed to a degree suggestive of psychosis. He used abusive and obscene language. He was increasingly irritable and aggressive and deliberately wet his bed and poured tea on it. On February 20, 1947, however, Dr. Ritchie Russell thought that he was responding to firm treatment and with skilled care should improve greatly. There was considered to be no indication for operation and Dr. Russell judged that in spite of his mental backwardness and antisocial behaviour it should be possible to bring him up to be a useful member of society. On psychiatric examination in March, 1947, Dr. Wyatt found a mental age (revised Stanford Binet scale) of 4 years 10 months (I.Q. 74) and on performance tests a mental age of 5 years. The scores showed a marked degree of scatter, indicating emotional instability, and his behaviour on testing confirmed this. Dr. Wyatt noted a disturbance of emotional control, in some respects almost psychotic, and felt this might be related to a possible extension of the trauma, as shown on the radiographs, to the hypothalamus. From time to time, he found, the patient exhibited "brief flashes of fairly normal intelligence" which lapsed almost at once, and his view was that the boy was certifiable under the Mental Deficiency Acts and the outlook unfavourable for any appreciable improvement.

He was placed in various special educational establishments and his father made representations, and as a result, at the age of 15, he was awarded a 100% disability pension on account of his injury and its consequences. This fact does not seem to have been disclosed to the boy then or later: nor, indeed, does he appear to have been told anything of the injury. He left school at 16 and was employed in a laundry for eight months. After three months in a butcher's firm he worked for 13 months washing bottles in a dairy, and for a time earned £11 a week on a milk wagon. According to his subsequent account, he left the laundry and the butcher because of weakness and pain in his left arm, a disability he managed to disguise in the dairy by simply not using it. The welfare officer, however, could not recollect his mentioning this trouble at the time. During this period he was living at home, from which he ran away on four occasions, and he endeavoured to volunteer for the Army.

When medically boarded for National Service on October 22, 1958, he was given a Pulheems assessment of

P	U	L	H	E	E	M	S	C.P.
2	2	2	2	2	1	2	2	+2

He did not disclose, probably because he did not then know, that he had sustained the injury in infancy, nor that he was in receipt of a war pension. (His father received the payments of the latter as he was a minor.) Posted to a Royal Artillery unit at the beginning of January, 1959, the personnel selection officer noted his low mental grade and referred him to the area psychiatrist, who recommended him to be down-graded to M2.S3 "on grounds of great personal inadequacy", and noted "a solid summed illiterate S.G. 5". In consequence he was re-posted to the Armed Royal Pioneer Corps. Here he complained of pain in the left arm resulting from small arms drill. In the meantime his father had initiated enquiries with the Ministry regarding his service. He was admitted to a military hospital on September 11, 1959, for observation.

On physical examination nothing abnormal was detected. It was noted that although the patient complained of weakness in the right upper limb the power was good and the tone symmetrical. The fields were full, and acuity (uncorrected) 6/6 in both eyes. The Wassermann reaction was negative in both blood and cerebrospinal fluid; there were no blood cells in the latter, and protein was 25 mg. per 100 ml. Radiographs showed multiple opacities in the right fronto-parietal region. Some of these appeared to be bone fragments lying off the direct track of a foreign body which lay above the right orbit. The character and position of this are better assessed from the films taken immediately after the injury, in which the outline is sharper. The appearances are quite consistent with this foreign body being a piece of window glass, similar to that originally extracted at operation from the wound of entry. Dr. Russell was of the opinion that the injury resembled a right-sided leucotomy.

The E.E.G. report on May 21, 1959, was: A 10 c/s rhythm was dominant bilaterally and inhibited on eye-opening. Overbreathing produced no change. Within normal limits.

Mentally, he was found to be "of pleasant disposition, but very low intelligence". He was fully orientated in time and space. His reading was very poor. His recent memory was assessed as "fair", remote as "poor". On brief informal psychometric testing his performance was very poor, but without specific outstanding features. It was noted on June 16, 1959, regarding his general comportment during five weeks of ward life, that he showed no gross behaviour disturbance. On one occasion he was seen to partake of a neighbour's meal while sitting at supper. He tended to forget instructions, and, occasionally, to disobey them. He was dirty and unkempt. Just before discharge he burned his left hand by spilling petrol on it while filling a lighter and inadvertently setting light to it. The precise status of this "accident" was not determined.

More detailed psychological examination (R.C.O.) was undertaken with a view to detecting any signs of "frontal lobe" type of intellectual defect that might be present. He appeared dull and uneducated, but not disorientated within his own rather constricted environment. He could not, or refused to try to, draw a map of England to show where Oxford and Liverpool lie, but was able to draw an accurate plan of his ward to show the position of his bed. In the same way he was orientated with regard to the immediate past but hazy about remoter events. He was able to give a coherent account of the more superficial aspects of his life in the Army and previously of civil life, and of his attitudes to them. But closer questioning induced incoherence and he drifted off into other topics with which he was preoccupied.

Block designs (four blocks) were carried out quite expeditiously, he made appropriate changes to correct initial mistakes fairly adequately, and showed no perseverative tendencies. In the Vigotsky sorting test he was able spontaneously to sort by colour, and when asked to find a second method had no difficulty in sorting by shape. Asked to find a third way, he made an attempt, though inadequately, to sort by size. He sorted coloured wools (Goldstein-Scheerer test) as rapidly and effectively as a normal individual, showing no tendency to be either overcareless or overpernickety about the categories he adopted, nor did he lose track of the system he was using. His immediate verbal memory (sentence repetition test) showed fairly gross defect, with little capacity to improve over three successive trials of the same sentence. He was capable of immediate reproduction of simple line figures by drawing, without gross inaccuracy or loss of spatial framework.

The general impression was one of low-grade general intelligence without specific elements of defect of orientation, failure of "abstract attitude" or of "categoreal behaviour" (Goldstein), such as may commonly be found in adult patients with severe frontal damage or deterioration.

A fuller, formal, psychometric assessment was carried out on June 26, 1959 (M.W.). Performance on the Wechsler (WAIS) shows a verbal I.Q. of 79 and performance I.Q. of 59. Sub-test (standard) scores were as follows:—

H	Information	4
H	Comprehension	4
N	Arithmetic	7
N	Similarities	8
N	Digit span	7
H	Vocabulary	6
N	Digit symbol	3
H	Picture comparison ..	4
N	Object assessment	4

It should be explained that these scores are in each case to be related to an average adult score of 10. The left-hand column indicates in which tests the score holds or does not hold its pre-morbid level in general mental deterioration of organic origin.

There were no signs of any specific defects or any indications of traumatic as opposed to congenital mental defect.

His memory on the digit span test and on a test of delayed recall was quite normal for a person of his I.Q.

Performance on the Rorschach test was rather limited, probably due to his low I.Q. The only abnormal feature apart from this was an inability to form any constructions involving colour, a suggestion that he is unable to integrate emotional stimuli. There were occasional signs of tension, and a tendency to go for minute details in an obsessional manner, but not to an extent greater than that often encountered in youths of his age.

Discussion

The history of this boy presents a number of puzzling features difficult to reconcile on any single assumption. The trauma he suffered at the age of 5½ months must have caused very severe and extensive damage to the right frontal lobe. Figures 1 and 2 show tracings from the radiograph taken immediately after the injury of the shadow of the foreign body, and although no precise determination of its shape, size and position can be made from these pictures, Dr. W. M. Cowan, of the Department of Human Anatomy, Oxford, has been kind enough to try to assess which brain structures are likely to have been involved, by sectioning an adult brain in relation to the track of the foreign body and inserting a piece of cardboard to represent the latter. His conclusion is that the glass lies in the white matter above the orbital surface just anterior to the putamen and just lateral to the caudate nucleus. In reaching this position it may have cut through the tip of the anterior horn of the ventricle, but probably did not touch the tip of the temporal lobe. The track appears to lie frontal to the precentral gyrus, and the entire lesion seems clearly confined to the right of the midline.

Up to and including the age of walking and talking, experienced attendants were unable to

detect any evidence of interference with the patient's normal mental and behavioural development. Outspoken behaviour disorder, however, declared itself when he was about 3 years old. At this time his mother had just gained official sanction for relief from her responsibilities and the father was avowedly anxious to commit the child to institutional care. The material circumstances of his home at this time, too, were unfavourable. The extent of the behaviour disturbance may have been exaggerated by the father at the outset, but that it was gross and persistent was fully confirmed by doctors and nurses in 1947 when he was 6½ years old. Yet, apart from the cranial scar, there was a complete absence of any neurological or other physical consequence of his injury. Had this injury not been known of, nothing at this time would have contra-indicated a diagnosis of behaviour disorder with mental retardation or deficiency. And his personal and family history could scarcely have been thought inappropriate to this condition and indeed might well have been held responsible for it.

At the age of 18 the picture has somewhat changed in emphasis. The outstanding impression is one of low-grade mentality, whether congenital or acquired, with some suggestion of mild behaviour disturbance. He might be considered to have made a good recovery from an earlier behaviour disorder which bordered on the psychotic. Nevertheless nothing in his condition would have suggested revision of a diagnosis which made no appeal to cerebral trauma. Indeed the results of full psychological assessment would bear this conclusion out. No evidence of psychological defect specifically characteristic of frontal lobe damage was found. The deficit was of a generalized kind with no special incapacity to evoke abstract attitudes and to use categories.

Had this boy been mentally defective at birth to an extent that would account for his later condition, one might expect that this would have been manifest in retarded development of walking and talking. In fact, despite the handicap of a severe cerebral injury, he was said to have developed quite normally at this stage. Equally, if he had been normal at birth and it was the cerebral injury which later produced the behaviour disorder and intelligence defect, its effects might have been expected to include earlier retardation of development of speech and locomotion. The most reasonable conclusion would seem to be that the child's condition after the age of 3 was due to a combination of unfavourable factors, including poor upbringing, a cerebral insult, and possibly some congenital defect.

Whether or not the brain trauma has played any part in inducing his present condition, what stands out as clearly established is the association of an early massive frontal injury with and absence of specific mental defect of the type which might be expected to follow such injury in an adult. In this respect, the case bears out the contention of Hebb and of Russell that when massive injury is sustained at an early age the outcome tends to be lacking in specific features and the dementia to be less distinguishable from the global congenital type. But there is occasion for some surprise, in the light of Hebb's findings, that even though the lesion may have left the left frontal speech areas unaffected, no disturbance of language functions resulted. Hebb reports that early lesions not in the speech areas tend to result in a linguistic disability which manifests itself in low scores on verbal tests relative to those on performance tests. The opposite disparity is found in the test results in our case. To what extent this feature might support the view that the patient's dementia is not at all the outcome of his injury is not easy to decide.

Perhaps we may be permitted to conclude with a plea that all cases of infants sustaining severe cerebral trauma, whether or not there are manifest effects, should be carefully observed throughout their course, with full psychological assessment at appropriate intervals, and that the results should be published. Collation of the resulting data could afford a fresh approach to the intellectual functions of the brain.

We are much indebted to Dr. W. Ritchie Russell for the opportunity of studying this case and for permission to report upon it, and to Dr. Cowan for his anatomical assistance.

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OBSERVATIONS ON SELECTIVE LEUCOTOMY*

BY

WALPOLE LEWIN

From the Department of Neurological Surgery, Radcliffe Infirmary, Oxford

The time is an appropriate one to look back at the development of surgery for the relief of mental illness and to note some of the recent trends, for it is just a quarter of a century since this method of treatment became established. It is true that Burckhardt (1891) had performed some cortical excisions in the frontal and the temporo-parietal regions for mental illness, but this work was not followed up and it was not until 1935 when Moniz and Lima operated on their first patients that leucotomy as now understood began. The effects of frontal lobe injuries in man were known from the reports of the First World War, and Brickner had given a detailed account of frontal ablation in one patient (Brickner, 1934) but Moniz was particularly influenced by the work of Fulton and Jacobsen (1935) on frontal ablation in monkeys. These workers drew especial attention to the change that took place in a neurotic female monkey which after operation became placid and tame. Moniz and Lima operated on their first patient in 1935 and in 10 weeks, 20 such operations had been performed. The monograph describing the immediate results was published the following year (Moniz, 1936). Briefly the claim was that of the 20 patients, seven were cured and eight improved. Following this one can refer to the first phase of leucotomy when for the next 10 years the standard pre-frontal leucotomy was employed for the majority of cases. Some of these early operations were uncritical and were performed mostly on psychotic patients in whom, although the gross effects of the operation could be detected, it was not possible, except in a minority, to decide whether there were any finer changes of personality and intellect. The results obtained were illustrated by the review by the Board of Control of 1,000 cases (1947). The mortality in that series was 6%, and 35·3% of patients were discharged either recovered or improved. Of these 9·3% subsequently relapsed, giving an overall "considerably improved" figure of 26%. This has remained the average figure of worthwhile benefit to be derived in the psychotic group once stability after the operation, which may take up to two years, has been reached. It was noted then that schizophrenic patients stood only a 23% chance of improvement whereas manic depressive illnesses improved in 50%.

During the latter part of this first period two main factors came to light which damped the early enthusiasm for the operation. One was the occurrence in some patients after leucotomy of uraemic states or a more complex metabolic disorder leading to trophic changes including wasting, decubitus ulceration, and ultimate death. McLardy (1950), who described such a series of patients, noted that these changes were associated with posterior cuts, particularly those involving the corpus striatum. The second factor was that as the operation was extended to psychoneurotic illnesses and later to psychosomatic illnesses, that is to patients with otherwise well-preserved personalities, so the untoward effects of the operation on the intellect and the personality became more apparent. There followed several critical surveys of such effects after the standard leucotomy. Thus Partridge (1950) well summarized them by noting that these patients showed an inability to profit by experience and an inability to plan the future. There was a reduction of activity, lack of spontaneity and persistence. The patients showed a reduction in affect such as worrying less and were emotionally less disturbed with a reduction in restraint and the appearance of such features as greediness, selfishness, and tactlessness. Tow (1955), in a monograph summarizing the work of this first period of leucotomy, concluded that after frontal lobotomy there was a reduction in many functions, although loss in none, and warned against conclusions drawn by meticulous testing of one function to the exclusion of others. In particular he confirmed that pre-frontal leucotomy did reduce the intellect and ability to plan ahead and in general there was a loss of abstract thought and a tendency towards a more concrete life.

The end of this first period closed, therefore, with

*Based on papers read to the Royal Medico-Psychological Association in July, 1957, and to the Department of Psychological Medicine, Liverpool in March, 1958.

confirmation that leucotomy could benefit a proportion of patients who otherwise were condemned to an inveterate illness but also demonstrated that there were unwanted side-effects to the extent that if surgery was to be applicable outside this small group of patients, a more limited operation would have to be devised which would confer at least the same benefit with far less post-operative complications of all kinds.

The recent years have seen a trial of various limited operations on the frontal lobe, both by open and closed methods, in an attempt to solve this problem. Aside from the immediate practical necessity was the still unanswered neurophysiological question as to whether there was specificity of function within the frontal lobe.

Case Material

It is not proposed in this paper to describe in detail the various procedures which have been carried out but to illustrate this second phase of leucotomy by reference to two operations which have been practised in this department during the last 11 years. It seemed reasonable that selective leucotomies should be open operations wherever possible, not only in order to be more certain that the procedures in fact were limited, but also so that their effects could perhaps be more accurately applicable to the problem of frontal lobe function. The two operations have been orbital leucotomy and cingulectomy. In 1948-59, 115 such operations were performed in 113 patients. There was one death related to operation. This was in a patient with involutional melancholia who after cingulectomy developed cerebral infection and died from bronchopneumonia three months after operation. Eight other patients have died within the period of follow-up, six from unrelated causes, and two committed suicide, one in an unrelieved mental illness and one in a relapse after seven years' improvement following cingulectomy (*vide infra*).

Orbital Leucotomy

Evidence of the relation between the orbital cortex and emotional disturbance, and the suggestion that interference with the pathways of the orbital cortex would have a beneficial effect on emotional disturbances, characterized by depression and anxiety, have accumulated over the years. Kleist (1934) reviewed a large series of head injuries and concluded that injury to the supero-lateral aspect led to disturbance of intellect, and lesions of the orbital surface produced emotional changes. These observations were confirmed on a small but more thoroughly studied group of cases by Rylander (1939). In the experimental field Livingston, Fulton, Delgado, Sachs, Brendler, and Davis (1948) in Fulton's laboratory had shown that orbital ablation in monkeys led to decreased activity, tameness, and freedom from excessive fear. In man, Meyer and Beck (1945) and McLardy and Meyer (1949), from neuroanatomical studies on leucotomized brains, concluded that although clinical recovery was correlated with the greater lesion, there was some evidence to suggest there was a possible advantage in isolating the orbital cortex. Clark, Le Gros, and Boggon (1933) had demonstrated in cats the connexion between the medial portion of the dorsomedial nucleus of the thalamus, the hypothalamus, and the orbital cortex of the frontal lobe, and the studies of Meyer, Beck, and McLardy (1947) on leucotomized brains confirmed this in man, but showed that the projection was confined to the medial half of the orbital region. Spiegel, Wycis, Marks, and Lee (1947) showed that electrocoagulation of the medial nucleus of the thalamus produced good effects in the emotional sphere. This relationship between the dorsomedial nucleus of the thalamus and the orbital cortex could be demonstrated later by Ström-Olsen and Northfield (1955) who reported their findings in a patient who died from a systemic illness some time after a successful orbital leucotomy. The orbital surface had been undercut and there was degeneration of the medial part of the dorsomedial nucleus of the thalamus.

These connexions of the orbital cortex and its posterior part in particular have been associated with the concept of the "visceral brain". Economo (1929) felt that the cingulate gyrus was part of the cortical station for the autonomic system and Papez (1937) presented the hypothalamus, anterior thalamic nuclei, gyrus cinguli, hippocampus, and their connexions as a cerebral mechanism subserving elaboration of emotion and emotional expression. McLean (1949) developed this concept of the visceral brain to include the posterior orbital cortex and the temporal pole with the amygdaloid nucleus and this work has been supported by the experimental work of Fulton.

Results.—Orbital leucotomy was introduced by Scoville (1949). Our earlier results, together with a description of the operative details, have been described elsewhere (Tow and Lewin, 1953). At the beginning of the series the majority of patients were schizophrenics who showed marked tension, anxiety, or agitation. In the last six years or so, however, we have operated far less for schizophrenic illness than for affective disorders characterized by agitated depression, severe anxiety, or depression which have incapacitated the patients and failed to

yield to all other treatment. In these patients the overt illness has lasted at least two years, and in most cases for much longer. All these patients were considered by the psychiatrists under whose care they were to have a prognosis without operation which was virtually hopeless. In this series of 60 patients there were no deaths or operative complications. The results are summarized in Tables I and II. All but four have been followed up for at least two years after operation, and others for periods up to 10 years.

TABLE I

ORBITAL LEUCOTOMY FOR AFFECTIVE DISORDERS AND PSYCHONEUROSIS

Diagnosis	No.	Result		
		Greatly Improved	Some Benefit	No Improvement
Agitated depression	11	5	4	2
Depression	11	6	2	3
Anxiety and "tension" states	7	2	4	1
Obsessional neurosis	4	2	1	1
Anorexia nervosa	3	3	–	–
	36	18	11*	7
		29		

*Eight of these 11 patients are at home.

TABLE II

ORBITAL LEUCOTOMY FOR PSYCHOTIC ILLNESS AND PSYCHOPATHIC STATES

Diagnosis	No.	Result		
		Greatly Improved	Some Benefit	No. Improvement
Schizophrenia	19	4	7	8
Psychopathic illness	3	1	1	1
Manic depressive psychosis	2	1	1	–
	24	6	9*	9
		15		

*Six of these nine patients are at home.

Orbital Leucotomy in Psychotic Illness.—Of 24 patients with major psychotic illnesses, schizophrenia in 19, manic depressive psychosis in two and three patients best described as gross psychopaths, six have been considered greatly improved. This term indicates that these patients have left hospital and have returned home and are working. The quality of the improvement is such that four of the schizophrenic patients declare that they are cured and their relatives think so, too, but in such an illness it is wiser to avoid the word "recovered" or "cured". In the second group "some benefit" refers to patients who are undoubtedly much improved after operation; indeed five of the seven schizophrenic patients have returned home and the two who still remain in hospital are quieter, working, and joining in social activities. But in all these patients there is still a very obvious schizophrenic illness present and it would be wrong to class them as greatly improved, merely because several have been able to leave hospital. Of the other eight schizophrenic patients, although some are quieter and easier to manage, one would not consider this a worthwhile improvement from a surgical point of view and a justification for operation. Indeed three of these patients may be worse, for although relieved considerably of their tension and impulsiveness, they have remained since operation apathetic and unwilling to work within the hospital, and should be classed as failures.

Two points may be made about these results in schizophrenic patients. The first is that with the indications for operation as set out above, the results obtained by orbital undercutting (nine patients discharged from hospital out of 19) are at least comparable to those by standard pre-frontal leucotomy. The second point is that four of these patients obtained such a degree of improvement as to be considered by some to be cured. Attention in the past has been focused on percentage improvement to leaving hospital but it is surely important to study closely the so-called "cures" to discover why it is that they have done so well. It has been suggested that success or failure is unpredictable and in a schizophrenic illness leucotomy will improve a quarter of any selected group. Nevertheless, one should search for trends in the clinical pattern of these patients which might enable a firmer prognosis to be made as to the success or otherwise of a proposed operation. Thus in these four patients it may be significant that before their illness all had been individuals with good affect and there was nothing in these patients' earlier histories or in the family histories to suggest schizophrenic traits. Again, none showed the typical schizophrenic build; in fact, three of the four were rather short and stocky. The onset and duration of illness should also be noted, for in two cases the length of illness had been comparatively short, at about two years, and in the other two, although the illness had lasted seven and nine years respectively, both patients had previously been well adjusted. Other writers have commented before on the importance of basic personality in assessing prognosis and it would appear that in judging the likely response of a schizophrenic illness to operation, the basic personality of the patient, the family history, and the type of affective life before illness, may all be valuable pointers in addition to the accepted symptomatic indications of tension and aggression. The phenotype (Parnell, 1955) may also prove to be another helpful guide in adopting standards for operation.

Orbital Leucotomy for Affective Disorders.—Table II shows the results of 36 operations for affective disorders. No fewer than 18 of the 36 patients were greatly improved and a further 11 benefited, all but three being at home. Indeed in 12 it is pardonable to speak of recovery in that all the symptoms complained of before operation have gone, the patients are well adjusted to life, and their relatives consider them cured. There were seven failures, but in four this possibility was anticipated owing to the patients' poor personality background. Pointers towards a good prognosis after operation were a good personality before the illness, and where the illness was accompanied by some loss of weight (Knight and Tredgold, 1955). On the other hand the results in those patients with an inadequate or immature personality or where there was a strong hysterical element in the illness were less satisfactory.

These results, therefore, in depressive and anxiety states appear satisfactory, and improvement has been maintained now for periods up to 10 years and compare not only favourably with standard leucotomy but immeasurably better in that in none has there been any gross personality change or metabolic disorder associated with the more destructive operation. Older patients did well with orbital leucotomy and this series included three patients of 70 years.

The general pattern of recovery after operation was usually one of immediate change and in most patients it was possible to gauge within the first few weeks whether there was likely to be a good result or not. This differed from the immediate effects of cingulectomy to which reference will be made later. It was important, however, to arrange a rehabilitation programme for some patients who showed limited early improvement, for it was found that they could go on improving slowly for periods up to two or three years.

Complications.—Although clinical recovery has been mentioned it has been avoided in tabulating the results, for there is little doubt that although personality changes are mild after orbital undercutting and certainly much less than after the standard cut, yet they are present in practically every case. In the early post-operative period there may be definite disinhibition and euphoria, although in only one patient was it ever marked and this later settled down. As regards the long-term effects some of these patients when questioned said that they tired more easily, a few remarked that they were unable to plan ahead as well as they used to in the past, and some of the housewives noticed that whereas they used to be able to calculate their housekeeping expenses very easily before the illness, calculation took them longer although it was still accurate. We were particular to ask these patients whether they had lost anything they valued by operation and usually received a negative answer. It should be added that some of these patients were not highly endowed, but on the other hand within this group there were teachers, journalists, social workers, and the like who were able to return to their work, including university education. In particular no patient noticed any difference in his religious appreciation or experience. A number of these patients had undergone intellectual tests before and after operation and no significant intellectual impairment was found (Mittler, 1957).

Prolonged incontinence following this operation was not present, and indeed in only eight of the 60 patients did it ever occur post-operatively at all. In only one patient did it persist for a few weeks and interestingly enough that patient ultimately made an excellent recovery.

Some *increase in weight* after operation was by no means uncommon but in only three patients was it considerable. One patient increased in weight from 9 to 15 stone in the six years after operation. It should be noted that the three cases of anorexia nervosa responded well and showed considerable weight gains. Knight and Tredgold (1955) noted that the operative results were favourable where the illness was accompanied by a considerable loss of weight.

There was no example of metabolic or trophic disturbance. Ström-Olsen and Northfield (1955), however, described one case where the cut went more posteriorly than usual and involved the internal capsule and the caudate nucleus on both sides. In the post-operative period this patient exhibited the classical syndrome to die ultimately with extensive ulceration. This gives further proof of the evidence for the site of lesion which produces this disturbance and also emphasizes the care that has to be taken in estimating the depth of the lesion at operation. It is true that in the great majority of cases, this, when compared with the length of the orbital roof, is usually fairly constant. But as in Ström-Olsen and Northfield's case and it may well be in others, particularly where the skull is small or there is some other disparity, this may not be so, and at operation it is important to note the individual landmarks.

Epilepsy occurred post-operatively in a few patients (five out of 60), although in two there was but a single attack and three of the five patients had either had a fit before operation or the pre-operative E.E.G. had shown a frankly epileptic record. No patient went on to have frequent attacks.

Orbital leucotomy would therefore appear to be a satisfactory operation for some of the effective disorders and to have a low incidence of complications. Scoville (1954) has reported similar results, and in this country Knight and Tredgold (1955) found that of 52 patients 23 were markedly better, the best effects being on depression and anxiety, and Ström-Olsen and Northfield (1955) found that of 13 patients with tension and anxiety or depression, seven could be classed as recovered and three improved.

Cingulectomy

Experimental ablation of the cingulate gyri in monkeys (Smith, 1944, 1945; Ward, 1948; Glees, Cole, Whitty, and Cairns, 1950) resulted in marked alteration in emotional behaviour with lessening of aggression and increased tameness. Fulton in 1947, at a meeting in Glasgow of the Society of British Neurological Surgeons, mentioned in discussion that were it feasible, cingulectomy in man would seem an appropriate place for limited leucotomy. Accordingly the late Sir Hugh Cairns in 1948 began the operation of anterior cingulectomy, the evidence at that time being that it was the anterior part of area 24 which was more concerned than its posterior part, area 23. The technique has been described previously (Whitty, Duffield, Tow, and Cairns, 1952). Through a formal right frontal osteoplastic flap the cingulate region is approached alongside the falx cerebri and the anterior 4 cm. of the cingulate gyrus on each side is removed by suction, the blood supply and the rest of the frontal lobes being left intact.

Early Results.—At first 18 chronic deteriorated patients, mainly schizophrenics with tension and aggression, who were candidates for leucotomy, had the more limited operation of cingulectomy performed. The early results allowed three conclusions: that the operation was technically possible but could be difficult and was not free from risk, mainly due to the proximity of the anterior cerebral arteries; that a truly limited procedure could be carried out; that although it became apparent that cingulectomy was not an adequate operation for schizophrenia, the immediate lessening of tension in these patients, and particularly the improvement in any obsessional features which took place, together with the absence of any added gross personality or intellectual change, suggested that such a limited operation might be applicable to psychoneurotic illnesses and to obsessional neurosis in particular.

Recent Results.—Since that time 34 patients have undergone cingulectomy. Table III* shows the results in 26 patients with psychoneurotic illnesses who have been followed up so far for at least a year and some up to 11 years. Of 15 patients with obsessional neurosis, 13 improved significantly, seven markedly so. The two failures in this group were due probably in one to the fact that the operation was incomplete for technical reasons, and in the other because there were also associated hysterical features, always a bad prognostic sign for any form of leucotomy. It was interesting to note, however, that in the first of these failures, a patient with a lifelong obsessional illness, there was no improvement three years after operation, but in the fourth year she made an excellent recovery following further psychotherapy.

TABLE III

CINGULECTOMY FOR PSYCHONEUROTIC ILLNESS

Diagnosis	No.	Result		
		Greatly Improved	Some Benefit	No. Improvement
Obsessional neurosis	15	7	6*	2
Anxiety/obsessional	6	3	2	1
Depression/obsessional	5	1	2	2†
	26	11	10	5
		21		

*Of whom three were operated on less than two years, and are still improving. All at home.

†One patient relapsed after seven years during which time she was greatly improved.

The pattern of recovery of these patients after cingulectomy should be noted, for although in the immediate post-operative period there is an obvious lessening of tension, together with a transient Korsakoff confusion in some patients (Whitty and Lewin, 1957, 1960), other dramatic changes are not seen. The obsessional thoughts retreat gradually but progressively into the background and the drive behind them lessens.

The following case record is typical.

Illustrative Case Record (*No. R.I.* 207229).—This young woman, aged 29 years, had had an unhappy family background. Mild obsessive features appeared when she was about 8 years old. She was easily upset at school, and shortly after leaving had an illness attended by fear of eating and a good deal of loss of weight which sounded very like anorexia nervosa. The patient was married when she was 19 years of age but the marriage was never a success physically. The patient had increasing difficulty in coping with her mounting obsessions until eight years before operation when she suddenly informed her husband that she could carry on no longer and from that date until operation there was increasing incapacity with her obsessional illness needing intensive psychiatric treatment, mainly psychotherapy. The situation was reached where the patient was unable to do any housework. A complicated ritual accompanied getting up and

*One of these patients operated on for schizophrenia with aggression is not included in Tables III and IV.

dressing in the morning, which took nearly eight hours, and at night it would apparently take nearly four hours to get to bed. She also had a considerable fear of eating, although she still looked well nourished. The patient also feared that she might develop an undesirable sexual attachment, although this never actually occurred. In the period before operation there was a steadily mounting tension.

A bilateral cingulectomy was performed. In the immediate post-operative period the obsessive thought content remained unchanged but there were three differences. First the patient was quite content to remain in hospital, whereas before it was doubtful whether she would remain in hospital even for the short period before operation. Secondly she immediately began to eat better than she had done for the previous two years. The third change was some immediate lessening of tension and mild disinhibition, but this was no more than the difference between inclining to laugh rather than to grumble at minor upsets in her daily routine. The patient returned home a fortnight after operation and remained under psychiatric care as an out-patient and was seen at regular intervals thereafter.

Three months after operation the patient said that she felt she was now going up the ladder instead of down. The obsessional features were still present but were less, and she could do things which were quite beyond her before operation. She was able to eat well and she could now get herself dressed within an hour, which compared very favourably with the situation beforehand. Six months after the operation the patient was still improving and she was now doing all her housework; help in the house which had been provided for five days a week immediately post-operatively had now been reduced to one day a week. Moreover, she was able to do her shopping, and, previously having had to avoid all shops which had any mirrors, she was now able to go into one or two of them. She realized that she did still wash and change her clothes more than was normal, but it was within reasonable limits. One year after the operation the patient said she could not have believed that she would feel as well as she felt then. She realized that she was still obsessional but she was running her house entirely on her own. Moreover, she had taken a part-time job in a store in order to widen her interests, this suggestion having followed on the post-operative rehabilitation programme. Two years after operation, the patient felt she was entirely back to normal, she was leading a full life and she volunteered the information that such ritual as remained was more a habit than anything else. The patient looked well, and there were no obvious neurological abnormalities.

This improvement was maintained and when seen on the fourth anniversary of the operation, the patient had given up her job as now in addition to her housework she had taken up social work. A family bereavement had been felt appropriately. An increase of weight of nearly 3 stone at two years after operation had now been reduced to 1½ stone over the pre-operative weight.

The results in this particular group are worth emphasizing for the therapeutic effect is striking when one considers an operation in which only a small amount of brain tissue is removed. Moreover, the results appear superior to other limited procedures. Thus in Knight and Tredgold's series of orbital leucotomy only five of the 12 obsessional patients were benefited; Pippard (1955), when reporting on rostral leucotomy, found less than half improved (12 of 26), and Busch, Halmsted, Lund, Nevin, and Thelle (1955) gave similar results for orbito-medial undercut. Obsessional neurosis is notoriously refractory to most treatment and indeed the only other procedure which gives results superior to cingulectomy is the standard leucotomy, which in one series (Partridge, 1950) gave 20 of 24 patients improved. But this is at the risk of considerable personality change and as many patients in this group are highly intelligent, standard leucotomy is too high a risk to run, certainly as a first procedure.

In general the patients likely to respond best to cingulectomy are, as with orbital leucotomy, those who have had a full emotional life before their illness, and in whom the illness is of acute onset and particularly if related to some external stimulus. By the same token the prognosis has to be more guarded where obsessional symptoms have been lifelong, where the basic personality is immature, and in particular where depressive symptoms are also prominent. Excessive ritualistic behaviour is another indication for a cautious approach, although by itself it does not necessarily mitigate against a good result as indeed the case recorded above illustrates. Indeed the obsessional illness which is so severe as to demand operation is the one not infrequently associated with ritualistic tendencies deeply ingrained.

In addition to the 15 patients with obsessional neurosis there were 11 other patients, who although showing obsessional symptoms, had marked anxiety and/or depressive symptoms as well. It would appear in this group that the prognosis is good where anxiety is dominant but, as can be seen from Table III, if depression is a feature the results are not so good and where this factor is marked it would incline one to recommend an orbital leucotomy rather than cingulectomy. Indeed, there was one patient in this series who, after cingulectomy, returned to his work and did well for four years after a long illness of obsessional neurosis with mild features of depression, but then relapsed with an almost pure depressive illness which responded dramatically to orbital leucotomy. Another patient derived considerable benefit for seven years after cingulectomy but then relapsed and committed suicide.

In a third group have been placed seven patients in whom more recently cingulectomy has been

TABLE IV
CINGULECTOMY FOR AGGRESSIVE STATES

Diagnosis	No.	Result	
		Greatly Improved	Some Benefit
Epilepsy with aggression	4	2	2
Paranoia with aggression	3	3	–
	7	5	2

performed for relief of severe aggression either within the compass of a paranoid illness or in association with epilepsy (Table IV). This was of course a further logical development from the earlier animal work, and Le Beau (1952, 1954) had reported favourably on its effects in epileptic patients and those with considerable mental retardation, classifying 15 of 20 as good results. So far we have been similarly impressed with our few cases. Thus all our seven patients derived some benefit, five markedly so. Before operation they had been given a very poor prognosis and the prospect of indefinite retention in hospital. Three have returned to full work and the fourth, although still prevented from so doing by frequent epilepsy, has had no more antisocial aggressive attacks which previously had terrorized a neighbourhood.

Complications.—Among these 34 patients there were no operative deaths. There were two complications after operation. One patient developed a local osteitis of the bone flap which cleared subsequently with limited surgery, and in the other patient there was a transient phase of raised intracranial pressure due probably to venous thrombosis which also subsided satisfactorily.

The mild personality changes noted in these cases have been reported earlier (Tow and Whitty, 1953). These are even less than after orbital leucotomy but we think similar, although quantitatively less. In this regard we differ from Le Beau and Petrie (1952) who feel that the changes after cingulectomy are qualitatively as well as quantitatively different from other leucotomies.

Urinary incontinence for a day or two after operation was commoner than after orbital leucotomy although in all cases it had cleared within the first post-operative week. This sphincter disturbance may well reflect the relations between the autonomic nervous system and the cingulate areas.

The risk of epilepsy was small. Only two of these patients who did not have an epileptic history developed fits for the first time after operation. In one a single attack occurred on the fifth post-operative day, and in the other attacks of an inhibitory type began three months after operation.

The operation of cingulectomy is a significant one when considering specificity of frontal lobe function. The concept of the cingulate gyrus as the cortical representation of autonomic function and its connexions with the hypothalamus in the "visceral brain" is of course pertinent. In some of our patients operated on under local analgesia, the cingulate gyrus has been stimulated and vomiting, incontinence, and momentary arrest of respiration noted (Lewin and Whitty, 1960). Cingulectomy may interrupt a reverberating circuit formed by hippocampus, fornix, mamillary bodies, anterior nucleus of thalamus, and cingulate gyrus, and it is interesting that it is the obsessional disorder which seems to respond best of all to this particular operation.

Our present policy is to regard cingulectomy as the operation of choice for the classical syndrome of obsessional neurosis and also for the young patient with obsessional symptoms and a marked anxiety state where operation is necessary and where it is particularly important to have the least post-operative personality change: young, because in the older patient an orbital undercut is effective, and is a simpler and safe procedure.

Conclusions

It seems permissible at this juncture to draw a few broad conclusions. There is no doubt that there are now available limited procedures which will produce results at least comparable in benefit with standard leucotomy and without the serious side-effects of the more extensive operation. This paper has illustrated two of them. Standard leucotomy is rarely indicated as the first operation of choice and indeed it seems that the stage is now reached where if a limited procedure is considered unlikely to give considerable benefit, then surgery is not advisable and the operation of standard pre-frontal leucotomy can be abandoned. The difficulty at present is that one cannot predict with sufficient accuracy the full effects of leucotomy nor are the standards of selection of patients for operation secure. In such a distressing illness as schizophrenia, for example, the fact that a small proportion of patients will improve to a considerable degree means that the operation is called for both by psychiatrists and by patients and relatives. Yet this should not lead to further indiscriminate trial of operation but encourage a more detailed selection of those patients most likely to benefit. In recent years clinicians have already come some way with this in symptomatology, but there are other factors to consider, some indication of which has been given which it would seem wise to explore further. All would agree that surgery is not the treatment for schizophrenia as such and

the aim should now be to define as closely as possible the small group where in the present state of our knowledge surgery still offers considerable relief from otherwise incapacitating symptoms.

A limited operation is the procedure of choice where surgery for affective disorders is indicated. The results from various centres, together with the experimental evidence on which these operations are based, make cogent arguments for directing surgery to the orbital cortex for symptoms of anxiety and depression and to the cingulate gyrus for aggression and obsessional disorder. However, comparisons with other limited procedures are notoriously difficult to make and there is as yet no agreement as to what is the most appropriate operation for a particular disorder. The good results reported with other limited operations are significant when considering whether the differences in effect of these various operations are quantitative rather than qualitative or if there is specificity of function in the frontal lobe as some of these results would appear to suggest. Rostral leucotomy yields good results for affective disorders and this operation has been carefully analysed by Pippard (1955). It should be noted, however, that this author advises caution in performing the rostral operation for depression due to the risks of hypomania supervening. He found that half the patients showed some intellectual deficit, though usually mild. They were more frequent with the blind operation and absent with the open rostral operation. Petrie (1956) reported only minimal intellectual deficit after the open rostral operation, but McKissock (1951) abandoned the open approach for the closed procedure since the results of the former were indifferent with only 30% good results. These intellectual changes need careful comparison with the effects of other limited procedures, for previous work would suggest that the more the supero-lateral surface of the frontal lobe is involved the greater the chance of intellectual deficit. Orbito-medial undercutting has a high incidence of epilepsy, up to 16%, as indeed has topectomy of areas 9, 10, and 11 (Pool, 1949). Stereotactic techniques can produce results comparable to a standard leucotomy but not, as yet, consistent limited results.

The emphasis in this paper on the complications and the mild but definite personality and other changes which follow all limited procedures on the frontal lobe should not be allowed to distort the overall picture. It should not obscure the benefits that these selective operations may confer on a selected group of patients who have failed to respond to all other appropriate psychiatric measures, have been ill for many years, and are totally incapacitated by their illness and likely to remain so. Any operation on the normal cortex will lead to some change but this may only be detected if our standards of assessment are fine enough. In judging operative results, although loss has to be weighed against gain, it should be remembered that it is not always possible to assess accurately therapeutic loss and gain when comparing these patients before and after operation. The present reserve in this field of surgery is a healthy one; but until there is an alternative, selective leucotomy can relieve otherwise intractable mental suffering.

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THE SIZE AND GROWTH OF THE HUMAN OPTIC NERVE

BY

PETER E. SYLVESTER and KEVSER ARI*

From the Neuropathology Department, the Fountain Hospital, London

Marked agenesis or atrophy of the intracranial portion of the optic nerve is easily detected but, when these abnormalities are moderate or slight, their detection is often difficult and often creates a need to assess the size of the nerve during pathological examination of the nervous system. However, lack of measurements at different ages from birth to maturity have made this task hard to achieve and so it was decided to measure the diameters of the intracranial portion of a number of optic nerves. This paper reports the findings.

Published figures for the diameter of the nerve have been expressed in one dimension only as though the nerve had a circular cross-section. This is correct for the intraorbital part but, in the intracranial section, the more accessible part and the site of measurement in this study, is more often elliptical. Scammon and Armstrong (1925) measured the optic nerve just before the constriction at the bulbus oculi and reported the diameter to be 2·8 mm. at birth. Vierordt (1906) found the diameter of the adult optic nerve to be 3·2 mm. at a point 2 mm. behind the lamina cribrosa. The site of measurement reported by other workers is not clear. Keeney (1951) found the diameter to be 2·7 mm. at birth and 3 to 4 mm. at puberty. Hervouët (1958), without giving the number of cases observed, reported the diameter to be 2 to 4 mm. at 3 months and 3 to 4 mm. at puberty.

The square area of the cross section of the optic nerve was estimated in its intraorbital part in three cases by Salzer (1880) and found to be 7·03, 8·13, and 8·76 sq. mm. Donaldson and Bolton (1891) measured the square area of both nerves in 10 adults. Seven of them were males who had a mean cross-sectional area of 12·79 sq. mm. (9·07-17·37 sq. mm.); three females had a mean area of 10·46 sq. mm. (8·74-11·61).

Materials and Methods

Optic nerves of 210 patients came from various sources. Some were obtained from 12 premature infants whose mean birth weight was 2,023 g. (4 lb. 6 oz.), S.D. = ± 410 g. (14 oz.), of whom 10 were born alive and two were stillborn. Others were available from 18 mature infants whose mean birth weight was 3,398 g. (7 lb. 6 oz.), S.D. = ± 496 g. (1 lb. 1 oz.), of whom eight were born alive and 10 were stillborn. The brain of one premature infant of birth weight 910 g. (2 lb.), who lived 25 hours, had incomplete formation of gyri, otherwise all the infants' brains were well formed. The brains of the remaining 180 patients, mostly low-grade mental defectives from whom nerves were acquired, had been collected in the Neuropathology Department at the Fountain Hospital over a period of nine years. Many of the brains were light in weight and had pathological changes found in this field of study such as gliotic encephalopathy, lipidosis, and microgyria. A number had mongolism.

However, included in the total of 180 there were 26 brains which were of normal weight and showed no naked-eye abnormality. They were either of high-grade mental defectives or of mentally normal patients whose tissues were used for control purposes. Wherever possible, both optic nerves were measured but in many cases, because the brain had been dissected, it was only possible to measure one nerve. The material had been fixed in neutralized 10% formaldehyde B.P. in normal saline.

Measurements were made in a gauge specially designed for this survey. The gauge (Fig. 1) was made of two pieces of transparent acrylic sheet (perspex) 3 mm. (2/16 in.) thick measuring 30 × 6 cm. Adjacent edges of each piece had been accurately cut so that, when they were placed together, they formed a slender V, the sides of which opened to 1·0 cm. at a distance of 20 cm. from the angle, which was indicated as zero. One side of the V was calibrated in 10 divisions, each of which represented the distance in millimetres between the sides of the V. It was possible to subdivide the space between each division by 10 and measure to 0·1 mm. The two pieces of perspex were fixed rigidly by four screws to a brass plate at either end, the whole gauge being mounted on a stand.

The fixed nerves were removed from the brain, stripped of any extraneous tissue and inserted into the V of the gauge by being held at one end in forceps. Each nerve was measured at a point 3-7 mm. from the centre of the chiasma and was held vertically and moved down the gauge until its progress was gently impeded. Force was avoided. At this point the nerve is elliptical and so the major and minor axes of the nerves were presented to the gauge and adjustments made until constant readings were

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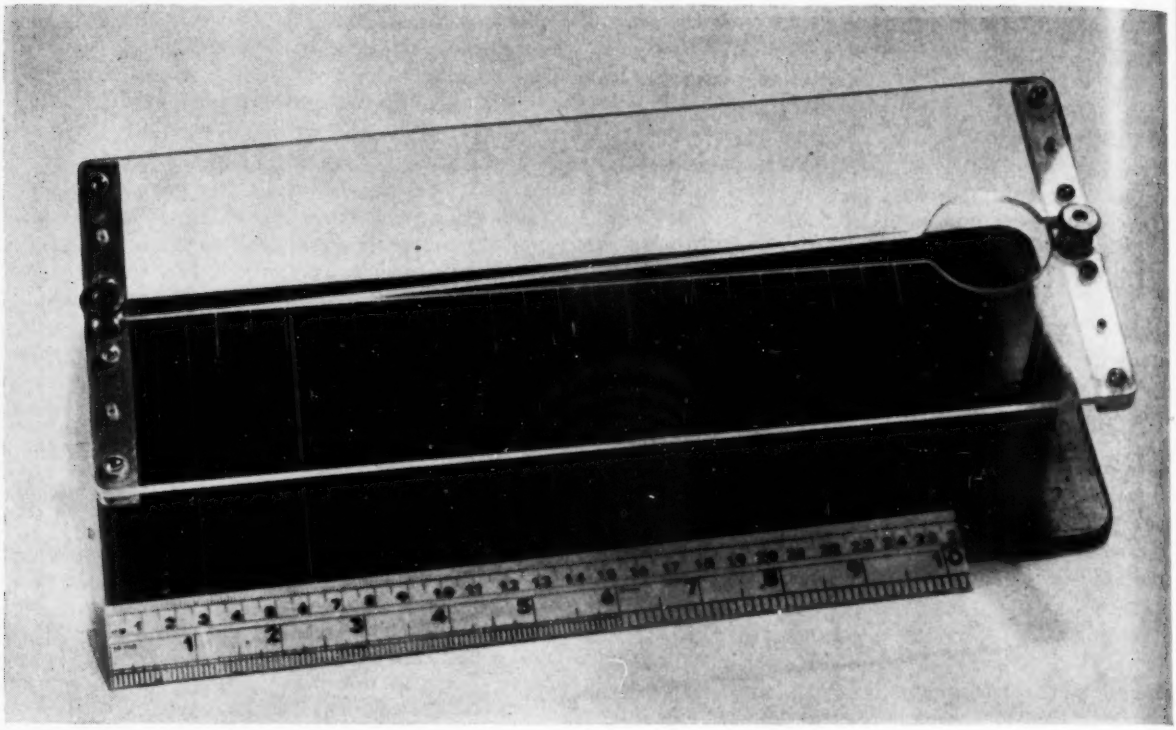

FIG. 1.—The gauge used for the measurements.

achieved in each diameter. Some of the infants' nerves were less firm than those of older children and could not be inserted into the gauge satisfactorily. They were measured by means of small geometrical dividers which were not found to be so convenient or accurate as the gauge. The measurements were grouped, according to the age of the patient, from birth to adult. (This group included patients of 12 years and older since the brain is often considered to attain adult size at about 12.) The area of the cut surface of each nerve was calculated from the formula π ab where a = half the major axis and b = half the minor axis.

Nerves were also measured from brains of 26 children who had optic atrophy.

Results and Discussion

The range, means, and standard deviation of the two axes and the area of the cross section of the optic nerves are presented in Table I; from these figures a graph (Fig. 2) was constructed. It will be seen that the curves, particularly that of the square area, indicate an increase in size from birth to the age of 4 years, after which the curve straightens. A possibility that the cases did not have a curve of normal distribution and hence could not belong to the same sample was tested. In the age groups 1 to 2 years, 2 to 3 years, and adult, it was possible

TABLE I

RANGE, MEAN, AND STANDARD DEVIATIONS OF MAJOR AND MINOR AXES AND CROSS-SECTIONAL SQUARE AREA OF INTRACRANIAL PART OF OPTIC NERVES DERIVED FROM 210 PATIENTS

	No.	Major Axis			Minor Axis			Area		
		Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.
Premature infants	12	1·5-3·0	2·50	±0·60	1·0-2·0	1·69	±0·47	1·18-4·71	3·41	±1·05
Infants newborn S.B.	18	2·4-3·5	2·82	±0·38	1·5-2·7	1·90	±0·18	2·36-7·43	4·27	±1·12
Infants 0-6 months	6	2·2-3·2	2·7	±0·36	1·7-2·2	2·05	±0·17	3·21-5·53	4·44	±0·86
Infants 6-12 months	6	2·3-3·3	3·03	±0·37	2·1-2·6	2·25	±0·17	3·8-6·74	5·39	±0·89
1-2 years	33	3·1-4·5	3·58	±0·336	1·8-3·1	2·43	±0·27	4·53-10·84	7·19	±1·56
2-3 years	25	3·0-4·5	3·81	±0·35	1·9-3·2	2·76	±0·356	5·42-10·60	8·34	±1·53
3-4 years	19	3·5-4·5	3·93	±0·31	2·6-3·4	2·86	±0·29	6·79-12·02	8·90	±1·47
4-5 years	18	3·5-4·4	3·96	±0·26	2·2-3·4	2·89	±0·363	6·88-11·75	9·12	±1·56
5-6 years	11	3·7-4·5	4·15	±0·17	2·6-3·5	3·01	±0·281	7·76-12·37	9·84	±1·48
7-10 years	16	3·0-4·6	4·03	±0·47	2·1-3·6	3·04	±0·431	4·95-12·37	9·76	±2·18
Adults	16	3·7-4·8	4·22	±0·26	2·6-3·3	2·99	±0·225	5·51-11·92	9·93	±0·33
Adults diseased	30	3·5-4·7	4·02	±0·39	2·1-3·9	2·80	±0·37	5·75-13·01	8·95	±1·99

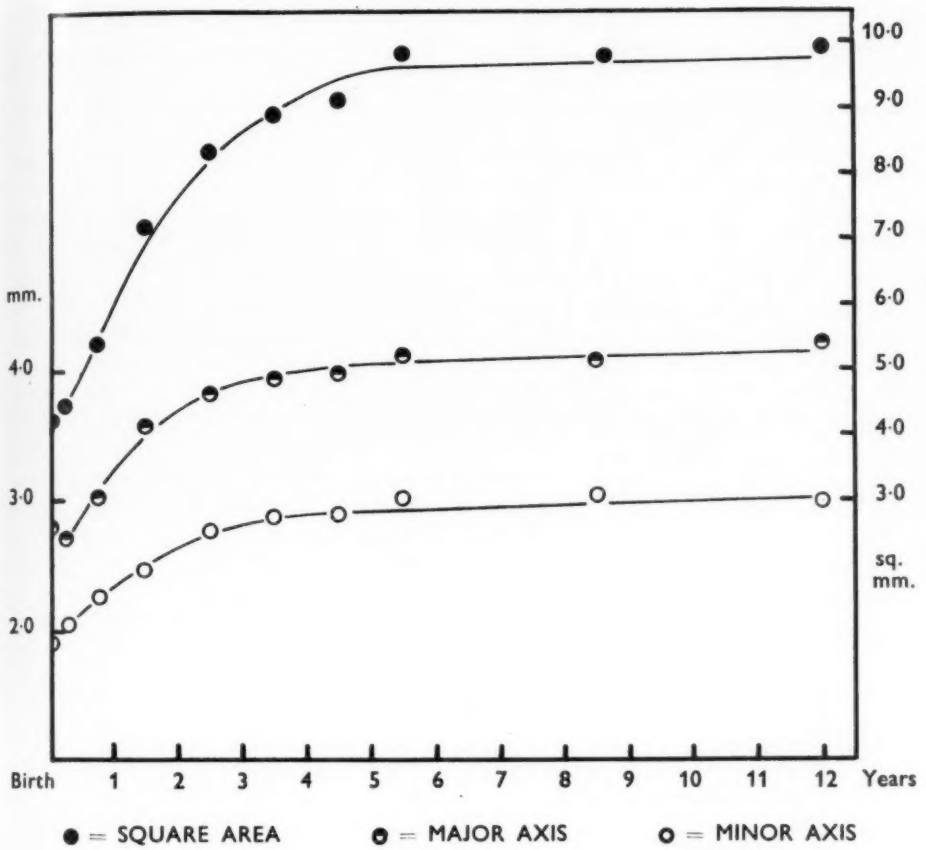

FIG. 2.—The cross-sectional area in square mm. (upper curve), the major axis (middle curve), and the minor axis in mm. (lower curve) of the optic nerve at ages from newborn to adult life, charted from measurements made on 210 patients.

to split each group into two subgroups. One of these contained the brains with known pathological changes, such as gliotic encephalopathy and lipidosis. The other group used as a control consisted of cases in which the brain appeared normal to the naked eye, control specimens from patients who had healthy nervous systems during life and had died from other causes, and mongol brains which had well-formed optic nerves. Student's t test and the F test were applied to these two subgroups. It was found that, in the age groups 1 to 2 years and 2 to 3 years, there was no significant difference between the control and pathological groups, so they were combined into one larger sample. However, in the case of the adults, the differences were on the borderland of significance, therefore only the control half of the sample was used in charting the graph. Differences due to sex were not significant.

Table II presents the measurements of the 26 brains of patients who had optic atrophy. The range and standard deviations of any particular age in the main sample seem to be large, which would make impossible the detection of moderate or slight abnormalities. Comparison with Table II suggests that severer abnormalities can be detected with certainty from 3 to 4 years since, at that time and beyond, the ranges of the comparative groups differ appreciably.

Alterations in the size of the nerves due to fixation were estimated by measuring 20 pairs of optic nerves in the fresh state and one month after fixation in similar formaldehyde solution to that used for the other optic nerves. Cross-sectional areas were calculated as in the main sample. These results are given in Table III. Nerves were not suspended during fixation and many of them became flattened and more oval so comparison of the changes before and after fixation were made on the cross-sectional areas. Thirty-four nerves shrank in the fixative and there was a wide range in the extent to which this varied, for instance 52·1% (in one nerve of Case 5) to 2·0% (in Case 12); three nerves showed no change and three nerves appeared to swell. The mean effect was that of shrinkage to the extent of 12·3%. Since the soft consistency of the unfixed nerves made handling, and thus measurements, difficult, there was a significant difference ($P<0·05$)

TABLE II

RANGE, MEAN, AND STANDARD DEVIATIONS (WHERE APPLICABLE) OF MAJOR AND MINOR AXES AND CROSS-SECTIONAL SQUARE AREA OF INTRACRANIAL PART OF OPTIC NERVES DERIVED FROM 26 PATIENTS WITH OPTIC ATROPHY

	No.	Major Axis			Minor Axis			Area		
		Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.
Infants 0-6 months	2	1·8-2·5	2·2	—	1·5-2·1	1·8	—	2·26-4·49	3·38	—
1-2 years	11	1·5-2·9	2·65	±0·36	1·1-2·4	1·80	±0·33	1·51-5·66	3·97	±1·10
2-3 years	3	2·6-2·9	2·7	—	1·6-2·8	2·1	—	3·27-6·60	4·76	—
3-4 years	2	2·6-3·0	2·8	—	1·8-1·9	1·9	—	3·68-4·71	4·20	—
4-5 years	3	3·2-3·5	3·3	—	2·2-2·7	2·5	—	5·53-7·92	6·66	—
5-6 years	2	2·9-3·2	3·1	—	2·0-2·3	2·2	—	4·71-6·03	5·37	—
7-9 years	1	—	2·5	—	—	1·5	—	3·27	3·27	—
Adults	2	3·0-3·4	3·2	—	1·7-2·2	2·0	—	4·18-5·18	5·0	—

TABLE III

MEASUREMENTS ON 20 PAIRS OF OPTIC NERVES IN THEIR INTRACRANIAL PORTIONS BEFORE, AND ONE MONTH AFTER, FIXATION IN 10% FORMOL-SALINE

Case	Sex	Age	Naked-eye State of Brain	Before Fixation				After Fixation			
				Diameters (mm.)		Square Areas (sq. mm.)		Diameters (mm.)		Square Areas (sq. mm.)	
				I	II	I	II	I	II	I	II
1	F	1 year, 2 months	Normal	4·5×3·2	4·0×3·2	11·56	10·05	4·4×2·4	4·0×2·5	8·30	8·17
2	M	2 years	Mongolism	4·0×3·4	4·7×3·5	10·68	12·07	4·5×2·9	4·5×3·1	10·84	11·56
3	F	3 years, 11 months	Multiple congenital malformations	3·6×2·8	3·5×2·8	7·92	7·92	3·8×2·5	3·6×2·5	7·76	7·35
4	M	4 years, 1 month	Mongolism	3·6×2·8	3·4×2·4	7·92	6·41	3·7×2·7	3·4×2·5	8·36	6·99
5	M	4 years, 4 months	Micrencephaly	3·0×2·5	2·9×2·4	6·13	5·66	2·8×2·0	2·7×2·1	4·40	4·84
6	F	4 years, 4 months	Normal	4·0×3·2	4·2×3·2	10·05	10·56	4·1×3·1	4·0×2·9	10·56	9·43
7	F	10 years, 6 months	Ulegyria	4·2×3·2	3·8×3·3	10·56	10·15	4·0×3·2	3·8×3·0	10·05	8·96
8	M	11 years	Inclusion body encephalitis	4·7×3·2	4·5×3·7	12·07	13·73	4·1×3·2	4·0×3·5	10·56	11·31
9	M	48 years	Normal	5·2×3·6	5·3×3·6	14·71	15·27	5·6×2·7	5·1×3·2	12·32	13·07
10	F	55 years	Cerebral glioma	5·4×3·2	5·5×3·4	13·57	14·96	6·0×2·8	5·5×2·9	13·20	13·20
11	M	55 years	Normal	4·4×3·0	5·2×3·0	10·37	12·25	4·5×2·5	5·0×2·6	9·40	10·21
12	M	55 years	Normal	4·6×3·2	4·6×2·9	11·56	10·84	4·8×2·5	4·9×2·5	9·80	10·21
13	F	57 years	Subarachnoid haemorrhage	4·8×2·8	5·2×3·3	10·56	13·89	4·2×2·5	4·4×2·4	8·58	8·30
14	M	60 years	Normal	5·1×3·2	5·6×3·2	13·07	14·08	5·2×3·1	5·5×3·2	13·07	14·08
15	M	61 years	Subarachnoid haemorrhage	5·6×3·2	5·3×3·2	14·08	13·57	5·7×2·5	5·7×2·6	11·85	11·85
16	F	62 years	Cerebral haemorrhage	5·0×3·1	5·0×3·5	12·56	14·14	4·9×2·7	5·0×3·0	11·00	11·78
17	M	63 years	Subarachnoid haemorrhage	5·3×3·8	5·3×3·8	16·12	16·12	5·3×2·6	5·5×2·5	11·03	11·44
18	M	64 years	Lobectomy of brain	5·6×3·3	5·5×2·9	14·96	13·20	5·6×2·7	5·3×2·4	12·32	10·18
19	F	72 years	Subarachnoid haemorrhage	5·5×3·0	5·5×3·0	13·20	13·20	6·2×2·4	6·2×2·4	11·69	11·69
20	M	89 years	Normal	5·3×2·8	5·6×2·6	11·88	11·44	5·5×2·5	5·3×2·6	11·44	10·61

between the experimental error of the unfixed nerves and that of the fixed nerves. It was conceivable that local conditions affecting the chemical and physical state of a nerve, for instance, oedema, amplified the differences between the fresh and fixed states. The age of the subject had no effect on the extent of the shrinkage. However, the fixed nerves being firm and easier to manipulate and revealing a smaller experimental error, suggested that the fixed nerves were a better medium on which to conduct a study of this sort. Nevertheless, it is conceivable that the variable effects produced by formalin fixation may give a misleading idea of the size of the nerve in the living condition.

The gradual increase in girth from birth till the age of 4 years is at variance with the view of Keeney (1951), who stated that the optic nerve was fully medullated at 3 months, by which time it had reached full size. Further statistical analysis of the sample signified that the sample was not homogeneous; for instance, there was a highly significant difference between the newborn period to the ages 1-2 years, a significant difference between age groups 1-2 years and 2-3 years, and an insignificant difference between age groups 3-4 years and 4-5 years. Thus the growth curve was a real and correct estimation of the facts, namely, that growth in thickness of the optic nerve continues from birth till the age of 4 years.

Since a post-natal growth curve of the optic nerve had not so far been reported in the literature, confirmation of the findings was sought amongst anatomical and physiological studies on other tissues. Todd, Beecher, Williams, and Todd (1940) compiled a growth curve of the weights of 69 pairs of eyeballs between birth and 21 years. They found considerable growth during the first year, continuing with diminished velocity to the third birthday. Eyeball growth, in general, followed brain growth. Their curve coincides closely with that of the optic nerve in this study. Rexed (1944) observed and confirmed that myelin sheaths and axis cylinders of

peripheral nerves increase in diameter during the first four years of life. Physiological development of the visual pathway continues for the first few years of life; for instance, Keeney (1951) reported that vision does not reach 6/6, or nearly so, until the fourth year. If these points are considered, it is reasonable to suppose that the optic nerve would continue to increase in size for the first four years of life, thus supporting the findings in this study.

Summary

Measurements of the major and minor axes were made on fixed tissues of the intracranial section of the optic nerves from 210 patients. The cross-sectional square areas were calculated. Brains of subjects from whom the nerves were obtained ranged from the newly born to adults, and thus it was possible to chart a growth curve. It was found that there was an increase in thickness of the nerve from birth till the age of 4 years, up to which time major growth occurs, and after which possible minor changes in growth continue up to the age 6-8 years. Twenty pairs of optic nerves were measured in the fresh state and after fixation for one month. A wide range of effects was revealed. The overall mean effect was shrinkage in fixative to the extent of 12·3%.

Optic nerves from brains of 26 patients who had optic atrophy were similarly measured and the findings given for comparison.

We wish to thank Dr. L. Crome for the stimulus he gave to this work, Mr. H. Freeman for designing and making the gauge, and Dr. J. Stern for help with the statistical calculations.

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THE ELECTROENCEPHALOGRAM IN CONGENITAL HYPOTHYROIDISM: A STUDY OF 10 CASES

BY

ERIC A. NIEMAN*

From Royal Southern Hospital, Liverpool

Cretinism in childhood, like myxoedema in adults, is a condition which is due to lack of circulating thyroid hormone, and for which there is specific hormone replacement therapy. It is a natural assumption that, provided therapy is begun early and continued in optimum dosage and without interruption, the results should be good. Unfortunately, although satisfying improvements in somatic development take place, the child's mental development is often unsatisfactory and difficult to predict.

In 1910, Siegert reported severe mental retardation in some cretins despite prolonged treatment. In 1929, Tredgold reported a number of cretins who obtained no mental improvement with thyroid. Bruch and McCune (1944) could find only three cretins with normal intelligence in a group of 23 treated cases. Other authors (Lucas, 1927; Gesell, Amatruda, and Culotta, 1936; Goodkind and Higgins, 1941; Wagner, 1943) agree that there is a poor relationship between therapy and mental prognosis.

Numerous reasons have been invoked to explain this discrepancy. Tredgold (1929) postulated two types of cretins: in the first the arrested development is due to lack of thyroid and the child is capable of normal mental and somatic development with thyroid replacement; in the second there is an associated primary amentia which cannot respond to thyroid although physical development is accelerated.

In 1885, Hadden reported cortical atrophy in the brains of two cretins, and Lotmar (1929) reported histological changes in the brain cells of cretins at necropsy, and concluded that when deficiency of thyroid occurs in foetal life it causes disturbances in the development of the brain.

The advent of electroencephalography provided an index of cerebral activity in the living patient. Kreezer (1937) studied the electroencephalograms of a few cretins (in a group of mental defectives, mongols, etc.) and reported a "relatively low frequency of alpha waves". Isolated cases of cretinism have also been studied by Jung (1950), who noted excessive slow activity, and by Schütz and Müller (1953).

The first report of electroencephalographic studies in a larger series of cases was by D'Avignon and Melin (1949). They studied 22 patients: eight with normal E.E.G.s, five with slight abnormalities, seven with markedly abnormal E.E.G.s, and two with unusually rapid activity for their ages. They remark that the E.E.G. in treated cases of congenital hypothyroidism seems to indicate that in cases with a low I.Q. (60 and under) the E.E.G. is markedly immature even when these patients had received adequate thyroid treatment and had shown normal somatic development. On the other hand, almost all psychically normal patients (I.Q. above 90) show a normal alpha rhythm.

Topper (1951) took E.E.G.s of seven cretins who had remained feeble-minded despite adequate treatment and of six cretins who were normal mentally. All the latter had normal E.E.G.s Of the seven feeble-minded cretins, five showed "diffuse cerebral dysfunction." She thought that

> "E.E.G. studies in infancy can be of prognostic import, since no amount of thyroid can bring about normal mentality in the presence of cerebral dysfunction, whereas if the E.E.G. shows a normally functioning brain, adequately pursued therapy can bring about normal mentality in congenital hypothyroidism."

Mai and Schaper (1953) found in their series seven patients with normal E.E.G.s after adequate thyroid therapy, and this correlated well with their physical and mental improvement. Thirteen patients, however, remained mentally retarded (some had been treated inadequately or sporadically): of these, 12 had abnormal records, for the most part, low voltage, poorly represented alpha activity, and excessive theta activity.

Chaptal, Passouant, Jean, Cadilhac, and Carli (1956) describe nine cases of "*myxoedeme pure*",

* Present address: St. Mary's Hospital, Paddington, London.

due to thyroid agenesis, and eight cases of "*myxoedeme encephalopathique*" (in which there is associated brain damage, proved in most cases by pneumoencephalography), which showed some degree of cortical atrophy and hydrocephalus. (It is interesting to note that earlier workers, including Mai and Schaper, 1953, had been unable to demonstrate any abnormality in this type of case on pneumoencephalography.) Chaptal *et al.* state that abnormalities of the E.E.G. in congenital myxoedema of childhood vary greatly according to the type of hypothyroidism, whether primary (thyroid agenesis) or secondary to an encephalopathy. In the former case the cerebral disorder is manifested by a delay in maturation of cerebral electrical activity. In the latter case there are often major signs of cerebral dysfunction with localized irritative abnormalities such as those encountered in cerebral atrophy in children (often high-voltage delta waves and spikes).

It appears, then, that previous workers agree that there are changes in the E.E.G. in many cases of untreated hypothyroidism in childhood, though there is no distinctive pattern of change. Increased theta activity and low voltage have been most commonly suggested as indices of lack of thyroid secretion. Most of the cases reported have been of E.E.G. changes in treated cretins, or of untreated cretins in later childhood and adult life. There are no detailed reports of the E.E.G. picture in infant cretins. The first three cases described in this paper were all diagnosed, and the E.E.G.s obtained, under the age of 6 months. They show in the waking state an unusually regular theta activity of remarkably constant amplitude and frequency, little artefact, and a noticeably small amount of delta activity. These records might be regarded as unusually mature for the child's age, though mental development in each case was delayed. Low voltage is a feature of two of these records only, and I would suggest, as in adult hypothyroidism (Nieman, 1958), that the mental torpor renders prominent and regular the dominant rhythm. The absence of dysrhythmia, paroxysmal activity, or spikes indicates probably a good mental prognosis if therapy is adequate. Cerebral development *in utero* (under the influence of maternal thyroxine) has presumably been normal; the E.E.G. changes at 3 to 6 months of age may be due to the direct effect of reduced cerebral metabolism rather than to retarded cerebral development. Thyroid therapy instituted at this stage should permit of normal mental growth and maturation of the E.E.G.

Case Reports

Case 1.—J. O'H, a girl, was seen at the age of 3 months. She had a cretinoid appearance, a protuberant abdomen, an umbilical hernia, dry skin, and was constipated. Radioactive iodine studies showed considerable hypofunction of the thyroid and the serum cholesterol was 775 mg.%. The E.E.G. shows the mixture of delta and theta activity that one expects at this age although probably the theta activity is somewhat more prominent than usual for a child of only 12 weeks. It was notable, however, that we obtained a complete record almost entirely free from artefact, the baby being unusually quiet. The dominant frequency was a 4 per sec. theta rhythm with an amplitude of 20 microvolts.

Unfortunately, she contracted a severe gastro-enteritis, due to *E. Coli* 0 111, a few days later, developed bronchopneumonia and died. At necropsy she was found to have a very tiny thyroid, the picture being one of agenesis of the thyroid, and not a colloid type of gland. There was no abnormality in the brain.

Case 2.—S.F.G., a girl, was also diagnosed as a cretin at the age of 3 months. A full-term normal delivery, she had never really thrived from birth. Radioactive iodine studies showed a maximum uptake of less than 2%, and the serum cholesterol was 90 mg.%. Radiographs of the spine showed a slight "slipper deformity" of L.2. The bone age was normal. The E.E.G. showed little artefact; on the whole a rather flat trace with short bursts of 2½ c/s delta activity with an amplitude of 35 microvolts. With thyroid extract she has been making excellent progress to date; unfortunately, I have not been able to obtain a repeat E.E.G.

Case 3.—C.F., a girl, aged 5 months, was delivered normally at full term. She appeared to develop normally until the age of 4 months, when it was noticed that she was having only one motion per week. Her face was puffy, her hair fine and smooth, and her feet were very cold (in June). The tongue was protuberant and she had a pot belly with an umbilical hernia. Her head control was not good though she could sit with assistance. She held toys but she did not pass them from one hand to another. She seemed interested in her surroundings.

An E.C.G. was of low voltage, with isoelectric T waves. A radiograph of the spine showed slight "slipper deformity" of the body of L.1 and slight central "beaking" of the body of L.2. The serum cholesterol level was 182 mg.%.

Assessment by a clinical psychologist suggested a developmental age of 20 weeks compared with a chronological age of 25 weeks. The E.E.G. (Fig. 1) shows a remarkably regular and stable 4 c/s rhythm in all leads with an amplitude of up to 100 microvolts. When the E.E.G. was repeated (Fig. 1a) she had been having thyroid, grain ½, daily for four months and was aged 10 months. She was doing well though she was still recognizable as a cretin. She was alert, warm, friendly, and interested in her surroundings. She held her head well and was sitting. She was having one, sometimes two, motions a day. The E.E.G. is now much less regular. The dominant rhythm has speeded up to 5 c.p.s. (75 microvolts) and there are some more rapid waves. A third record at the age of 1 year showed no further change.

This stability of the theta rhythm is seen not only in infancy but at other ages in untreated cretinism. The next case illustrates this regularity in a child of 3 years and 8 months, in whom thyroid therapy produced a rapid change in the E.E.G., and is developing normally in spite of late diagnosis.

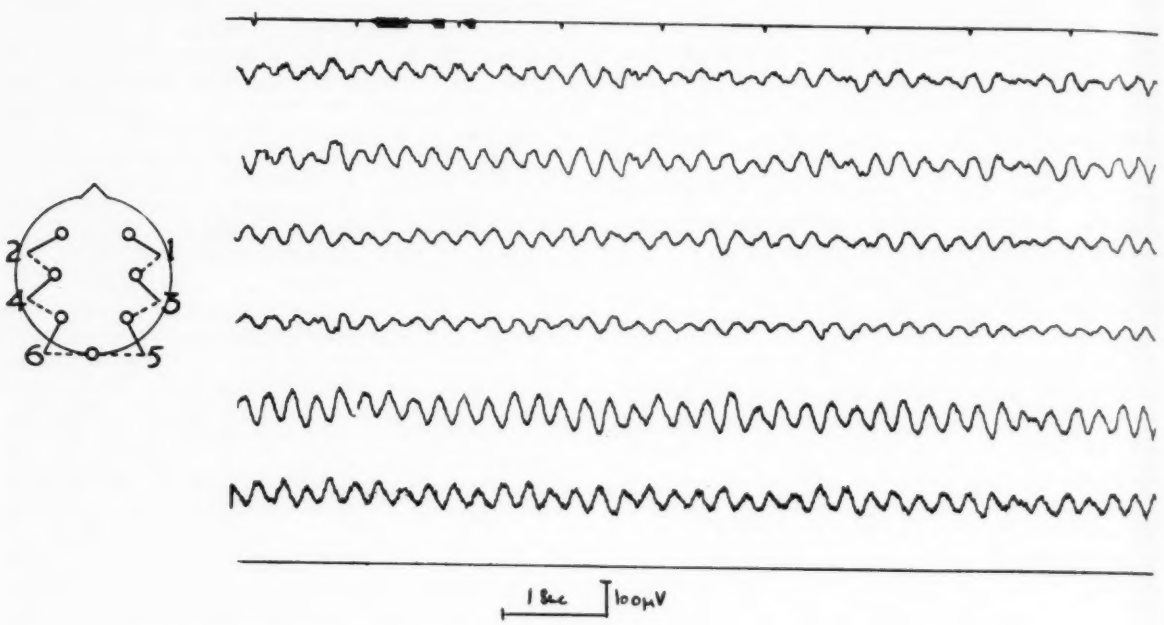

FIG. 1.—Untreated cretin aged 5 months. A regular, synchronous and symmetrical 4-4½ c/s theta rhythm.

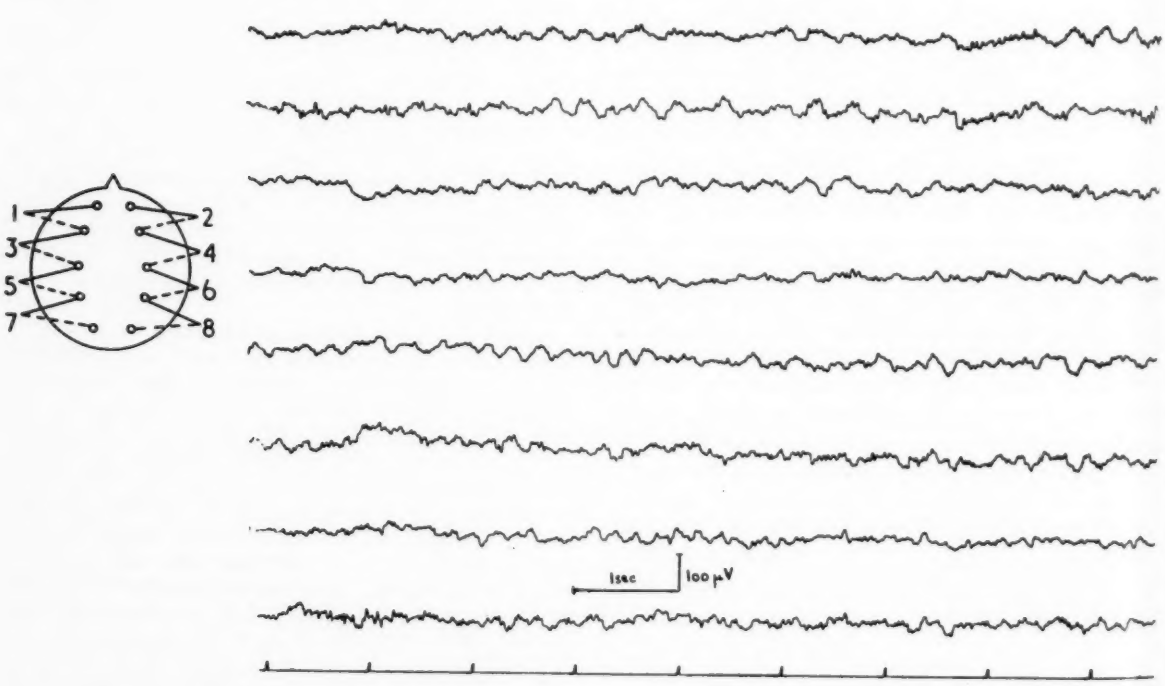

FIG. 1a.—Record after four months' treatment with thyroid, grain ½ daily. More irregular 5-6 c/s rhythm with some fast activity.

Case 4.—L.K., a girl, aged 3 years and 8 months, sat up at 8 months. Teething began at 6 months but the teeth were carious. She began to walk at 2 years. At the age of diagnosis she could say simple words only, could not dress herself, was incontinent of urine, but could feed herself with a cup and spoon. Her bowels opened twice a week. She was pale and puffy-eyed, with a dry skin, and looked like a cretin. Her bone age was 6 months. The E.E.G. shows a regular mixture of 3½ and 4 c.p.s. activity with an amplitude up to 75 microvolts. A repeat E.E.G. after only five weeks' treatment with L-thyroxine sodium, 0·1 mg. daily, shows considerable change. There is now a dominant 8-9 c/s occipital alpha rhythm as well as theta, and a very little low amplitude delta activity. This child now, at the age of 7 years, is normal for her age in weight and height, goes to school, and is said by the school teacher to be average for her age in class. She is having 0·25 mg. of thyroxin daily.

Case 5.—A.M.R., a boy aged 8, had a similar type of record, immature with a stable theta rhythm. He was diagnosed in infancy as a cretin, but was treated sporadically and inadequately with intermittent thyroid, grain 1 daily. He was slow at school, lacked concentration, was constipated, and below average height for his age. The record shows a fairly regular theta rhythm of 5-7 c/s with occasional bursts of higher voltage of 4 c/s theta rhythm (up to 75 microvolts). He has improved considerably since thyroid dosage was increased and given regularly, and is in the correct class for his age at school (though near the bottom of that class). A further E.E.G. has not been obtained.

Delay in diagnosis, however, although it does not preclude improvement both somatic and psychic on treatment, may yet determine a failure of the child to keep pace with its fellows. Progress may be steady and continuous but may fail to make up the ground that has been lost, as in the next case.

Case 6.—A.M., a girl, diagnosed as hypothyroid in June, 1954, at the age of 5, has a twin sister (heterozygous) who is normal (F.M.). Angela (the cretin) had been noticed to be much slower than her sister Felicity, and although heavier, was about 2 in. less in height. She walked at 18 months, was continent by 20 months, but at the age of 5 was still slow in speaking, lethargic and placid. Her hair was coarse, her voice deeper than her sister's, and her abdomen prominent. The bone age was 1 year, and the serum cholesterol 350 mg.%.

The E.E.G. (Fig. 2) of A.M. (cretin aged 5) shows a mixture of delta and 4-5 c/s theta activity. There is little visible alpha rhythm. The E.E.G. of F.M., the normal twin aged 5 (Fig. 2a), shows, in contrast, an 8 c/s alpha rhythm with only a little low amplitude theta rhythm anteriorly.

The records of the two girls were repeated three years later when they were 8 years old. Angela appeared mentally alert, spoke normally, and, by herself, would not have been recognizable as a cretin. But she is two classes below her sister in school, and is still plumper and slightly shorter (1½ in.) than her sister. Her progress, in other words, has been good, but still lags behind her twin sister. It will be seen that the E.E.G. traces remain very different. The record of Angela (Fig. 2b) shows still an

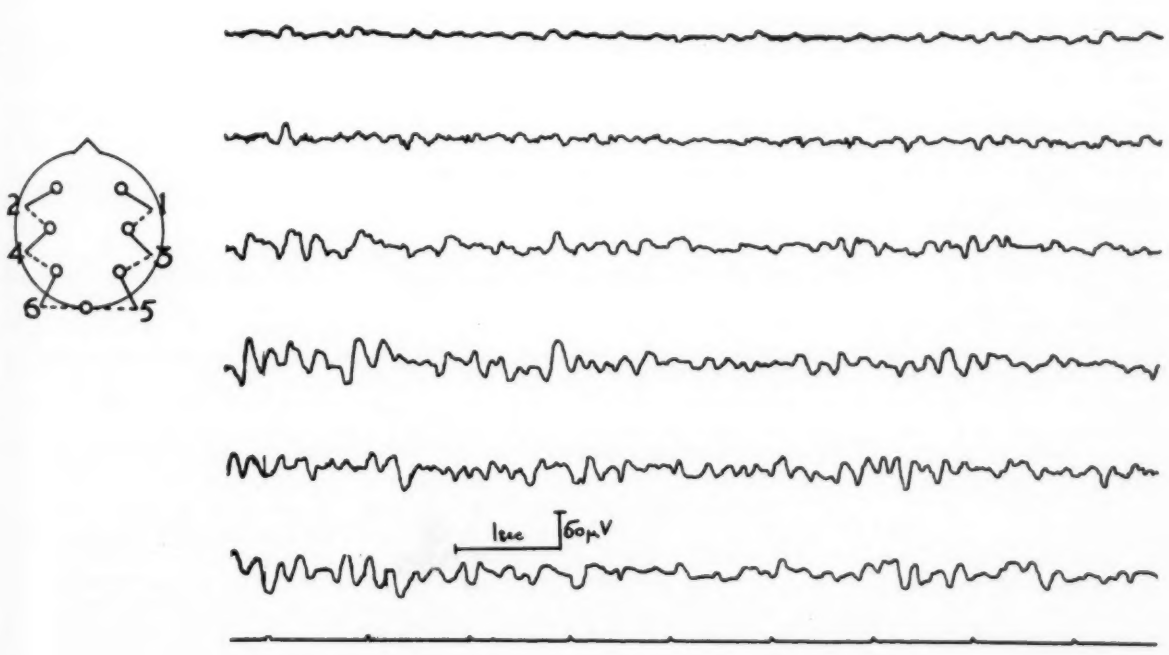

FIG. 2.—Untreated cretin (A.M.) aged 5. Mixture of delta and theta rhythms.

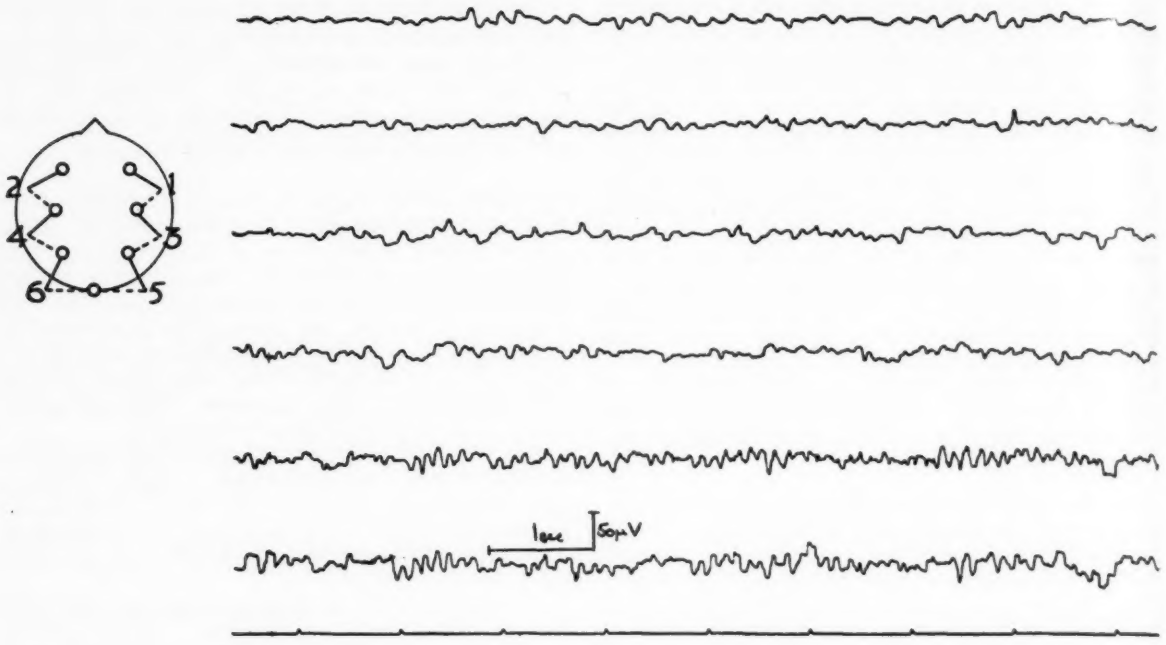

FIG. 2a.—Patient's twin sister (F.M.) at same age. Well formed 8 c/s alpha rhythm.

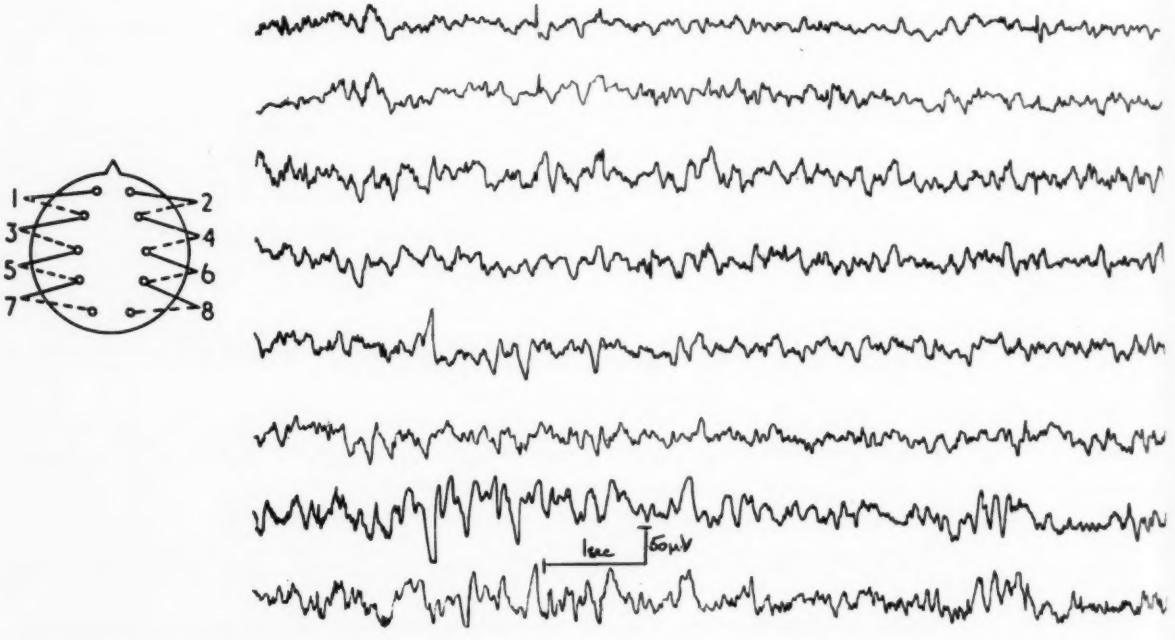

FIG. 2b.—A.M. after three years' treatment (aged 8). Irregular delta and theta waves with scanty 8 c/s alpha rhythm.

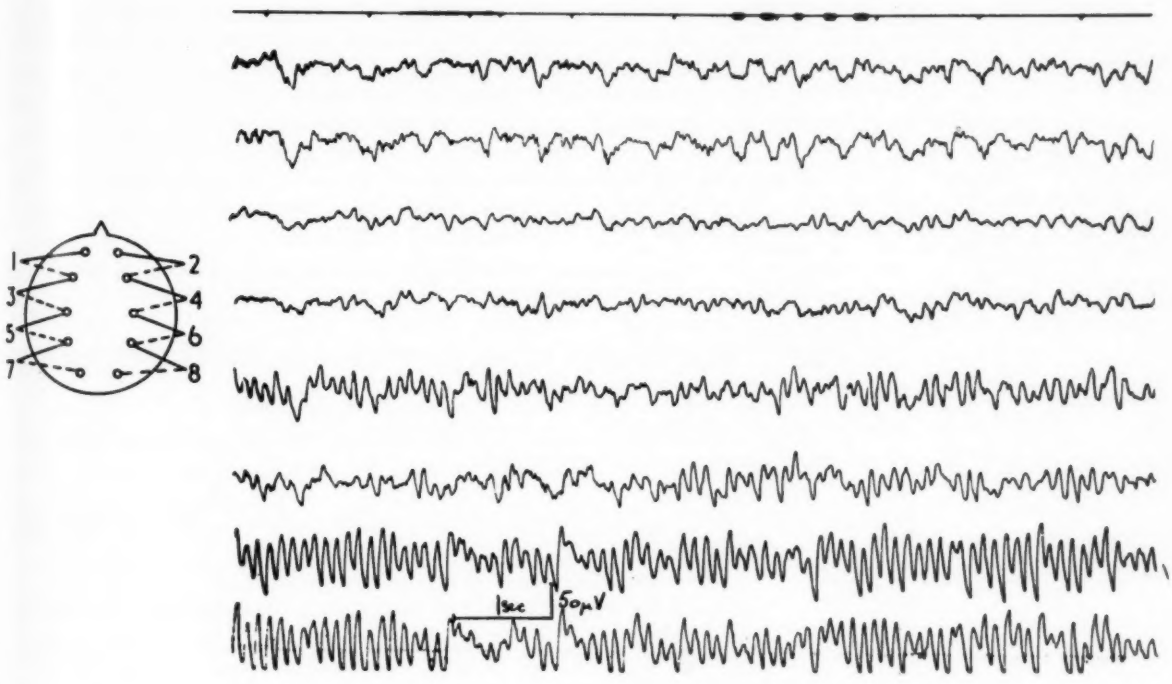

FIG. 2c.—F.M., aged 8. Well developed 9-10 c/s alpha rhythm and little slow activity.

irregular mixture of delta and theta activity with only a very small amount of 8 c/s alpha rhythm, whilst that of Felicity, her twin, now shows a well-developed 9-10 c/s occipital rhythm and only a little slow activity anteriorly (Fig. 2c). In the case of Angela, one would give a very guarded prognosis of ultimate mental attainment.

The next two cases are of children in whom mental progress has been less fortunate and there is definite evidence of retardation. In one of the two patients fits have occurred.

Case 7.—V.W., a girl, was a post-mature baby, delivered by Caesarian section, who was diagnosed as a cretin at the age of 5 months, and began to receive thyroid at that age. Her physical progress was good, but mentally her progress was very slow. An E.E.G. was first obtained at the age of 2 years and 2 months. She could not stand, said only a few single words, and, although having thyroid grain 2¾ daily, was still somewhat dull and lethargic.

The E.E.G. showed a poorly-developed occipital trace consisting largely of theta waves, with a little delta activity. In addition, throughout the record there was constant rapid activity with irregular spikes in the frontal leads, especially on the right. At the age of 4, although some mental improvement had occurred, she was still obviously retarded in that speech development was poor. Physically, she was normal, in fact above average height for her age. The E.E.G. shows that while there is now a good deal of alpha activity posteriorly, the frontal rapid activity remains.

Case 8.—R.G., a boy, was started on thyroid at 3 months and it was given regularly until 20 months, when his mother discontinued it as she thought it was not doing any good. However, given in higher dosage, he improved again. The first E.E.G. was performed at the age of 4 years. At this time his somatic development was satisfactory, and he was active and alert. The E.E.G. showed a dominant 7½ c/s rhythm, with some slower activity throughout the theta range. It might be regarded as a normal record for a child of this age.

At the age of 5, he had a major fit, which lasted 15 minutes. (At this time he was taking thyroid grains 5, daily.) Two weeks later an E.E.G. was obtained. Although this record is perhaps not grossly abnormal for a boy of 5, it shows no improvement compared with the previous record of a year ago, and there is more slow activity present, with a tendency for the 4 c/s theta activity to occur in short bursts. This boy's progress has continued to lag behind normal, and now, at the age of 8, he is still very obviously retarded, is enuretic, and has had one more fit.

Case 9.—E.J.S., a boy, aged 9, presented as a case of dwarfism due to masked hypothyroidism (see Bloch-Michel, Tubiana, and Brizard, 1957). His school progress was said to be satisfactory, but he was not as active as the other children, was constipated, and had frequent bronchitis. His height was 41 in. and his

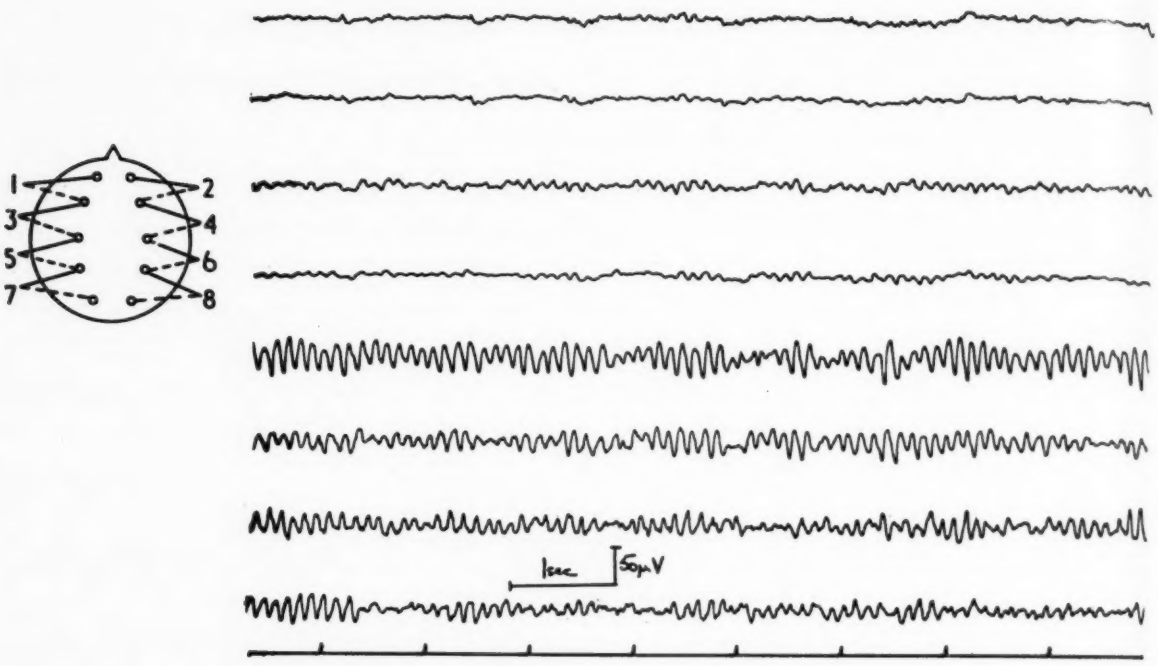

FIG. 3.—Cretin aged 33 (no thyroid treatment for 10 years). Normal 9 c/s alpha rhythm.

weight 44 lb. His skin was pale, but there were no cretinoid characteristics.

An E.C.G. was of low voltage. Haemoglobin was 76%, showing orthochromic anaemia. Trypsin was found in the faeces, but no excess fat. Blood calcium, phosphorus, alkaline phosphatase, and urea were normal. Serum cholesterol was 203 mg.%. The Wassermann reaction was negative. Bone age was 3 to 4 years.

The E.E.G. shows a fairly well-developed 8-9 c/s alpha rhythm, with a good deal of 3-4 c/s activity tending to occur in generalized bursts, an abnormal record for his age. Treatment with thyroid was begun and produced definite improvement. He now has more energy, is more alert in school, his bowels are regular, and in six months he has gained 2 in. in height. His E.E.G., repeated five weeks after starting thyroid, shows an improved alpha rhythm and less slow activity; there was no paroxysmal activity in the record.

Case 10.—M.C., a woman aged 33, was treated from early infancy with thyroid, with benefit. During adolescence she received thyroid sporadically, stopped it at the age of 23, and when I first saw her, she had received no thyroid for 10 years. She was mentally slow, with slow speech, had a dry coarse skin and hair, and a gruff voice. Her pulse rate was 58 per minute, the reflexes sluggish, and the ankle jerks absent. Her height was 54 in. and her weight 6 st. 4 lb. Her B.M.R. was —10% and —25%. The serum cholesterol was 200 mg.% and the E.C.G. was of low voltage with flat T waves. Radioactive iodine studies showed virtually no uptake, and the serum protein-bound iodine was 0·042% per litre.

The E.E.G. (Fig. 3) shows a largely 9 c/s alpha rhythm, well-developed and sustained (amplitude 50 microvolts), with some 8 c/s alpha rhythm and a little 10 c/s alpha rhythm, a normal record. Treatment with thyroid, grains 3 daily, has produced remarkable clinical improvement. She is more alert, her features have changed, and she has responded, in fact, as one would expect a case of adult myxoedema to respond. Her E.E.G. four months later shows an increase in the dominant frequency of the alpha rhythm to 10 c/s, but, otherwise, no significant change. It appears in this case that treatment in childhood had allowed of normal development of the E.E.G. and it would seem unlikely that there was any associated cerebral agenesis.

Discussion

One may conclude that in pure hypothyroidism, maturation of the E.E.G. proceeds *pari passu* with mental development in the adequately treated case, and may become normal. On the other hand, patients with pronounced mental defect who remain retarded on adequate treatment usually present abnormal records, the likely explanation being an associated cerebral dysgenesis. Topper (1951) considers that the age at which treatment with thyroid is begun may also play a part, and Mai and Schaper (1953) distinguish between athyroidism and hypothyroidism. They consider that in the former, delayed thyroid therapy may produce irreversible cerebral changes, whilst in the latter, the presence of minimal

thyroid secretion may produce the clinical picture of cretinism but prevent an irremediable mental retardation. There is no doubt that in some cases thyroid administration produces dramatic improvement in the E.E.G. (see Case 4) whilst in others (see Case 7) little maturation takes place and abnormalities persist. In further cases, mental improvement and some maturation of the E.E.G. may both take place, yet both lag behind normal (Case 6). There are still many unsolved problems, and larger series of cases are required of cretins diagnosed in infancy and followed carefully throughout childhood.

Summary

Review of the literature has shown that in treated cretins there is often a discrepancy between physical growth and ultimate mental achievement. This has been attributed to a number of factors, of which a co-existing amentia in a certain proportion of cretins is the most likely. An irreversible post-natal failure of cerebral development due to delay in instituting thyroid therapy may also account for some cases.

It has been shown that electro-encephalography may provide an index of mental progress in these children, and indicate the mental prognosis. Electro-encephalographic studies have been made in 10 cretins and the traces correlated with clinical observation. In three children, the initial records were performed under the age of 6 months.

The records in untreated cretins show an unusual stability, regularity, and freedom from artefact, in the waking state. Treatment produces a faster and more irregular record. Paroxysmal activity, spikes, or undue rapid activity suggest associated cerebral dysgenesis and a poor mental prognosis.

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THE ELECTROENCEPHALOGRAPHIC DIAGNOSIS OF MANIFEST AND LATENT 'DELIRIUM' WITH PARTICULAR REFERENCE TO THAT COMPLICATING HEPATIC CIRRHOSIS

BY

JOHN LAIDLAW[1] and A. E. READ[2]

From the Department of Medicine, the Postgraduate Medical School, Ducane Road, London

In a previous paper in this journal (Laidlaw, 1959), one of us discussed the potential value of assessing the generalized electroencephalographic (EEG) abnormalities which were found in those general medical disorders which did not affect the brain primarily, and described a visual method of expressing these abnormalities in the form of frequency patterns. Although it was felt that there was a place for this simple method, particularly in small EEG departments, it was admitted that it took time, was dependent on the experience of the observer, and provided only a limited amount of information. It was proposed that future work should be based on some form of automatic analysis.

This paper explains the system which was developed for quantifying and grading information about the rhythmic background activity of the EEG, whether normal or abnormal, obtained from a modified and simplified electronic waveform analyser, and describes the application of this system to a particular clinical problem.

The system of analysis has been applied to a variety of those general medical conditions in which the EEG is affected and it is clear that the changes which occur are not specific to any particular condition. One may postulate that there is a disorder of the metabolism of deeply placed structures of the brain. The EEG follows a fairly well-defined series of changes over a continuum from normal consciousness to deep coma (Laidlaw, 1959). There is at first a gradual reduction in the frequency of the rhythmic activity which may be preceded, accompanied, or immediately followed by a partial failure of alerting conditions to reduce or maintain the reduction of this rhythmic activity. Later, when the background rhythms have fallen to between 4 and 6 cycles per second (c/s) larger slower waves of delta (under 4 c/s) frequency appear, at first occasionally and usually anteriorly, but gradually increasing in frequency and distribution until they come to dominate the record from all areas.

Certain patients with hepatic cirrhosis form an important group in which these changes occur. They are liable to episodes of confusion or alteration of consciousness (Adams and Foley, 1953) which we will term 'delirium'. A factor in the production of this delirium is the absorption of nitrogenous products from the gut (Sherlock, 1958), which are either inadequately detoxicated by a damaged liver and/or reach the brain in abnormal quantities through collateral portal systemic venous channels. We will use the term 'encephalopathy' to describe not the acute episode of delirium but the underlying state which makes certain patients liable to develop such episodes. It has been established (Dawson, McLaren, and Sherlock, 1957) that reducing the nitrogen content of the bowel by low-protein feeding or by sterilization with an antibiotic such as neomycin is useful for the acute phase, the delirium, and also reduces the liability for such a phase to develop on provocation, that is, reduces the encephalopathy. Contrariwise, high-protein feeding or the addition of nitrogen-containing compounds, such as ammonium chloride, makes delirium worse and more likely to develop: it increases the encephalopathy.

It is important for the clinician to know whether or not a patient with hepatic cirrhosis suffers from encephalopathy and, if so, to what extent, that is, under what conditions of diet or treatment he may be at particular risk of developing delirium. In severe cases of encephalopathy there may be permanent clinical, psychological, or electroencephalographic abnormalities, but in these cases the diagnosis is seldom in doubt and the electroencephalographic evidence is merely confirmatory. In those milder cases where the diagnosis is doubtful the EEG, while providing very early evidence of

Present address: [1] Department of Surgical Neurology, the Royal Infirmary and Western General Hospital, Edinburgh.
[2]Department of Medicine, Bristol University.

developing delirium (Read, Laidlaw, Haslam, and Sherlock, 1959), may be unable to detect a latent encephalopathy.

The technique to be described is based on provoking delirium in patients with hepatic encephalopathy and in using the EEG changes produced by this provocation as an index sufficiently sensitive to enable the provocation to be kept well below the level at which the patient would be exposed to the slightest risk.

Morphine was chosen as the provocative agent because it has been reported as producing delirium in patients with hepatic disease (Fagin and Thompson, 1944; Murphy, Chalmers, Eckhardt, and Davidson, 1948). Preliminary tests showed that small doses were perfectly safe. It has been reported as producing in normal subjects no EEG changes other than those of drowsiness or sleep (Greville and Heppenstall, 1950; Wikler, 1954; Andrews, 1941).

As the normal subject passes from full wakefulness through drowsiness to light sleep the EEG changes are well established (Davis, Davis, Loomis, Harvey, and Hobart, 1938; Dement and Kleitman, 1957) and are different from those of increasing delirium. Occasionally interpretation is difficult when drowsiness is a feature of the delirium and the EEG changes of the two conditions coexist. The findings to be reported suggest that in all subjects the changes produced by morphine are nearer to those of increasing delirium than of increasing drowsiness. However, it is not the purpose of this paper to discuss the differentiation between the sleep-wakefulness and delirium continua of EEG change, and such a differentiation is unnecessary since we are concerned with the differential EEG responses between patients and in the same patient under various conditions. We are satisfied, however, that the EEG changes produced by morphine are sufficiently similar to those produced by the early stages of delirium for the criteria of such changes to be directly compared.

General EEG Method

All records were made on an eight-channel Ediswan machine with filters for 75 c/s and time constant at 0·3 sec., and were analysed with a B.N.I. low frequency waveform analyser produced and specially adapted by Faraday Electronic Instruments Ltd. This analyser consisted essentially of 12 resonant circuits with centre frequencies at 2, 3, 4 and so on up to 12 c/s with 50% reduction $\pm$ ½ c/s and at 17 c.p.s. with 50% reduction $\pm$ 1½ c/s. The output from these circuits was lead to storage capacitors whose charge during a chosen epoch was read off from a meter in arbitrary units: these readings will be referred to as 'activity at such and such a frequency'. The outputs from those six circuits which showed the greatest activity were also lead back to an intermediate stage of the Ediswan EEG machine to give a direct write out of six channels of waves as they occurred at each of these frequencies (Fig. 1). The numerical value of the arbitrary units depends on the gains and adjustment of the analyser but is irrelevant since all the derived measures are proportions. It is convenient to adjust the analyser so that an input of 1 volt from a low-frequency sine wave oscillator gives a peak calibration reading of 10 microamps. It is important to adjust the gains on the analyser so that the maximum reading obtained lies within that part of the scale which is linear. The errors due to fluctuations in the apparatus lie well under 5% and may be ignored.

Two channels of primary EEG were recorded from the antero- and postero-lateral aspects of the non-dominant hemisphere. The activity from the posterolateral channel was fed to the waveform analyser. For each record 10 epochs, each of 15 seconds, were analysed. There were four types of epoch:—

S. 1-5. From 15 to 30 sec. after shutting the eyes.

O. 1, 2. From 15 to 30 sec. after opening the eyes. The patient lay on a couch in a dimly lit room and his gaze was directed towards a blackboard 2 ft. square and 6 ft. away on which were 100 small light bulbs in 10 rows of 10, centred 2 in. apart. No lights were switched on.

L. 1, 2. From 15 to 30 sec. after opening the eyes. As in O. 1, 2, but with 20 to 30 lights switched on to form a pattern.

Lc. From 0 to 15 sec. after opening the eyes. A different pattern of lights was presented on the board and the patient had been instructed to start to count the lights as soon as he opened his eyes and to call out the answer as soon as he had finished. The number of lights was adjusted to the patient so that he took rather longer than 15 seconds to count them.

The epochs were always arranged in the following order: S.1, O.1, L.1, S.2, O.2, L.2, S.3, S.4, S.5, and Lc. For each 15-second epoch the activity at each frequency was read off the analyser meter. A typical epoch reading might be:—

Cycles per second—

2	3	4	5	6	7	8	9	10	11	12	17

Activity in arbitrary units for S.1—

5	5	6	7	7	10	22	42	16	8	4	4

From this data the following calculations were derived.

Dominant Frequency—The frequency at which there is most activity $\pm$ a skew figure which is obtained by dividing the difference between the sums of the activities at the two frequencies above and below the main frequency by the activity at this frequency and multiplying by 100. In the example above the dominant frequency for S.1 would be:

$$9 - \frac{(10+22)-(16+8)}{42} \cdot 100 = 9 - 19$$

Change in dominant frequency is then expressed in units. It has been found that if the dominant frequency lies midway between two frequencies, the skew figure usually

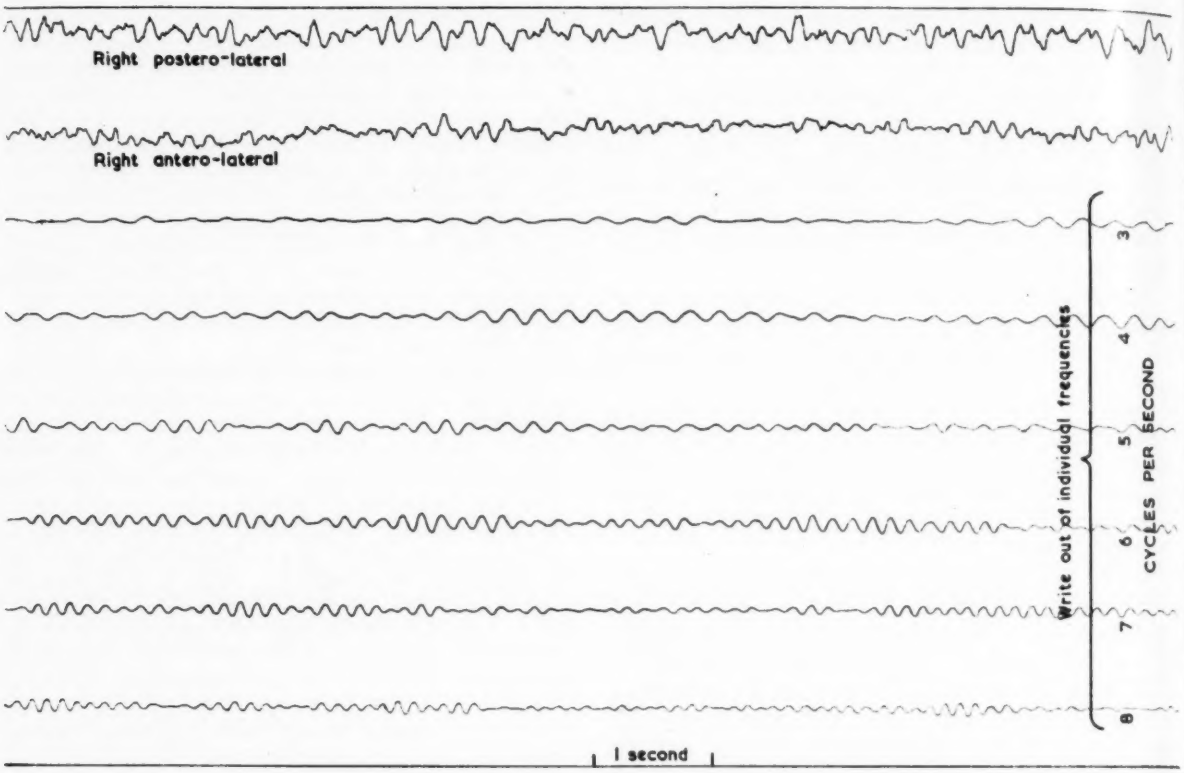

FIG. 1.—Case 8 with known encephalopathy. Moderate generalized abnormality in pre-morphine record. Channels 1 and 2 show the primary EEG tracing from the postero- and antero-lateral aspects of the right hemisphere. Channels 3-8 show the write-out from the analyser of waves as individual frequencies from 3 to 8 c/s.

lies roughly 75 units ± with respect to the lower or higher frequency. Therefore, in making calculations of frequency shift a figure of 150 units has been allowed for a full cycle per second. Thus a change from a frequency of 9 + 19 to 8 − 32 is measured as 19 + 150 + 32 = 201 units. Dominant frequencies are calculated for each S epoch and for the mean of the 5S epochs.

Rhythmic Activity (RA).—The sum in arbitrary units of the activities at the frequency with the most activity and the two frequencies on either side. In the example above: RAS.1=42+(10+22)+(16+8)=98. These calculations are made for each epoch with the eyes shut (RAS 1-5), open (RAO 1, 2), while looking at the light pattern (RAL 1, 2), and while counting the lights (RALc), and for the means of the shut (RAS), open (RAO), and lights (RAL) epochs.

From these figures it is possible to measure numerically changes between epochs, records, and patients in terms of dominant frequency and rhythmic activity under different conditions.

Two types of record are not suitable for purely numerical measurement and are best assessed by combining analysis with inspection of the direct write-out of the analysed frequencies and the visual method previously described (Laidlaw, 1959).

Records Dominated by Discontinuous Delta Activity.—Electronic analysis of such activity is apt to be unreliable since the tuned circuits respond to rhythmic activity rather than to occasional waves (Burch, 1959), and, since activity measured on the analyser is the product of number of waves and amplitude, it is possible to get spurious high readings at low frequencies due to underlying low amplitude background wobble or artefact.

Desynchronized Records Containing Little Rhythmic Activity.—The presence or absence of change is best assessed from the direct write-out of what activity there may be.

For descriptive purposes EEG generalized abnormalities may be classified according to the following criteria:—

Severe abnormality..dominant frequency under 4 c/s (within delta range).

Moderate abnormality..dominant frequency between 4 and 6 c/s.

Mild abnormality..dominant frequency between 6 and 7 c/s.

Borderline..dominant frequency between 7 and 8 c/s.

Normal..dominant frequency between 8 and 13 c/s (within alpha range).

In any large series of controls it will be found that most records will be normal, a number borderline, and a few will show a mild or possibly even a moderate abnormality (Brazier and Finesinger, 1944). This method of classification is of some value for describing single records but when there is little or no clinical evidence of delirium, the EEG is likely to be normal or borderline, perhaps sometimes showing a mild abnormality, and a single record has little diagnostic value. However, it is at this stage that the EEG is very sensitive to alterations in cerebral metabolism and the measurement of EEG changes may be of great value whether expressed quantitatively in terms of dominant frequency and RAO (L or Lc), or in terms of grades of change as are described later.

Clinical Application

Problem.—To contrast the EEG responses to small doses of morphine in patients with and without hepatic encephalopathy and the responses in patients with hepatic encephalopathy under different conditions of diet and treatment and to develop therefrom a method of assessing in doubtful cases the presence and extent of encephalopathy.

Method

Fifty-nine patients (Table I) were classified clinically as follows:—

Group E.—These are patients with hepatic cirrhosis who have had established episodes of delirium, or alteration of consciousness, sometimes referred to as hepatic 'coma' or 'pre-coma', such episodes being directly attributable to liver disease and being characterized by confusion, alteration of consciousness, sometimes increased tendon reflexes, 'flapping tremor', foetor hepaticus and, almost invariably, severely abnormal EEGs. These patients are considered to suffer from known encephalopathy with a tendency to develop delirium. Factors which tend to provoke delirium include infections, drugs, gastro-intestinal haemorrhage, and deterioration in liver function. The group is a heterogeneous one with patients requiring widely varying degrees of provocation.

Group C.—The control group consisted of patients without liver disease, termed controls, and those with various diseases of the liver said to have no encephalopathy because there had never been an episode suggesting delirium and there was no reason why such an episode should develop.

Group D.—These were patients with hepatic cirrhosis considered to have doubtful encephalopathy. This group includes, on the one hand, patients who, because of such factors as the state of liver function, age, or extent of collateral circulation, are considered as possibly liable to develop delirium, and, on the other, those who have a history of episodes suggestive of but not definitely shown to be hepatic delirium.

In 112 tests on 64 patients, EEGs were recorded immediately before and three hours after varying doses of morphine. Of these, eight tests have been excluded as follows: four tests (two patients) because the associated EEG changes of drowsiness made assessment impossible and four tests (three patients) because there were EEG abnormalities presumed to be due to another condition later diagnosed (disseminated sclerosis, epilepsy, and Hodgkin's disease). Table I shows the distribution of the remaining 104 tests on 59 patients (40 female, 19 male, aged from 19 to 76 years) according to clinical classification and dose of morphine. There were eight 'dummy' morphine tests in which no morphine was given.

The general EEG method already described was used. For the sake of simplicity and in order that the results for the whole series might be comparable, only two measures of change were calculated: units of dominant frequency change and percentage change in rhythmic activity with the eyes open (RAO). Deterioration, considered as reduction in dominant frequency and percentage increase in RAO, is expressed numerically and in terms of the following arbitrarily chosen grades:—

Grades of Change

Grade 4.—The appearance in the second record of high-amplitude delta waves which were not present in the first and which were sufficiently prominent to dominate the record.

Grade 3.—A reduction in dominant frequency of 150 units (1 c/s) or more with an increase in RAO of 25% or more.

Grade 2.—A reduction in dominant frequency of 50-149 units with an increase in RAO of 25% or more.

TABLE I
DISTRIBUTION OF TESTS ACCORDING TO DOSE OF MORPHINE AND CLINICAL GROUPING OF PATIENTS

Patient Classification	Clinical Group	No. of Patients	No. of Tests	Numerical Analysis Only	Dose of Morphine (mg.)			Grading of Pre-morphine Record				
					0	8	16	Normal	Borderline	Mild Abnormality	Moderate Abnormality	Severe Abnormality
Controls	C	8	8	5	0	3	5	8	0	0	0	0
No encephalopathy	C	14	17	10	4	9	4	15	2	0	0	0
Doubtful encephalopathy	D	20	41	36	3	32	6	32	5	3	0	0
Certain encephalopathy	E	17	38	29	1	34	3	17	8	6	7	0
Total		59	104	80	8	78	18	72	15	9	7	0

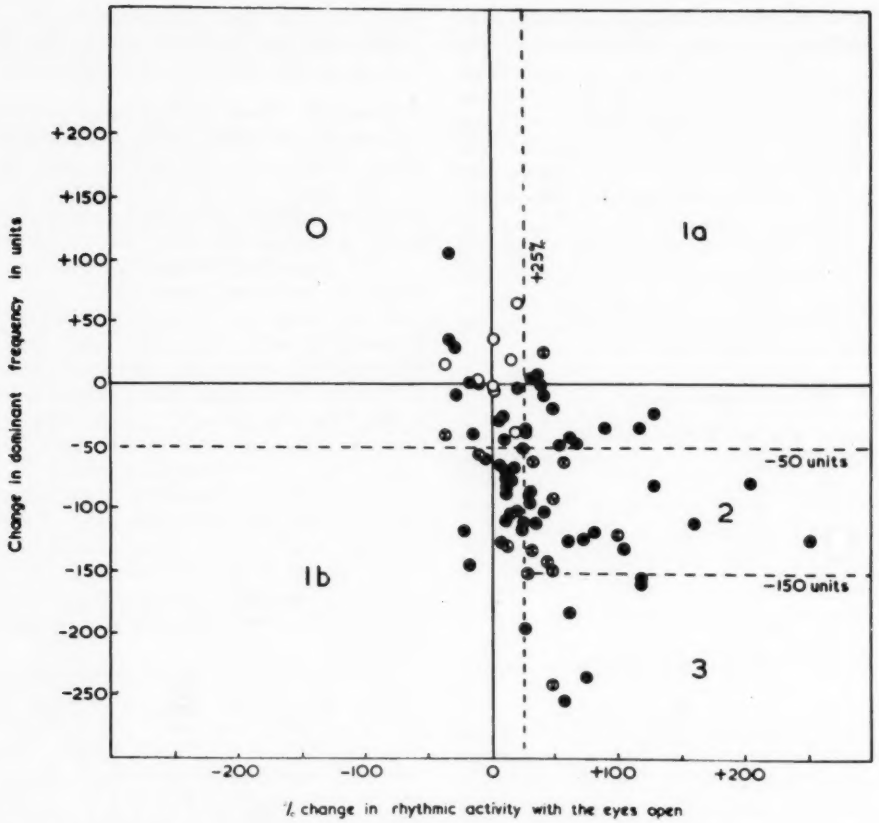

FIG. 2.—Results in the 80 morphine tests in which the EEG changes were expressed numerically. Each point represents unit change in dominant frequency plotted against percentage change in rhythmic activity with the eyes open for one test. 0 = no morphine, ● = 8 mg., ⊕ = 16 mg. morphine. The five areas into which the graph is divided correspond to grades of change 0, 1a, 1b, 2, and 3

Grade 1b.—A reduction in dominant frequency of 50-149 units without an increase in RAO of 25% or more.

Grade 1a.—An increase in RAO of 25% or more without a reduction in dominant frequency of 50 units or more.

Grade 0.—Records which do not show the numerical changes above or which, if not assessed purely quantitatively, show no change considered as significant.

Grade 1 has been subdivided because it was found that the first evidence of deterioration might be either increase in RAO or reduction in dominant frequency.

In certain cases (Table III) the tests were repeated under different conditions which are referred to as follows:—

P.—After three days' treatment with neomycin, 1 g. t.d.s., usually on 40 g. protein diet

Q.—After a 40 g. protein diet for at least seven days

R.—After a normal ward diet (about 70 g. protein) for at least seven days

S.—After a protein diet of 100 to 120 g. for at least seven days

T.—After ammonium chloride, 2 g. t.d.s. for three days, usually on a high-protein diet.

All comparisons between records are made in the direction of expected deterioration, *e.g.*, P—R = change between neomycin régime and normal diet. The addition of 'm' denotes a post-morphine EEG: thus R—Tm represents the EEG change between the pre-morphine record on ward diet and the post-morphine record after three days on ammonium chloride.

Results

To the right of Table I is shown the classification of the pre-morphine records. The seven moderately abnormal records were made during repeated tests on two patients in group E. It will be seen that the great majority (84%) of records are normal or borderline and that it would not be possible to decide from a single record whether or not a patient suffered from encephalopathy, *i.e.*, to place a group D patient in either group E or C.

In Fig. 2 unit change in dominant frequency is plotted against percentage change in RAO. It will

TABLE II

EEG DETERIORATION- EXPRESSED IN GRADES, PRODUCED BY DIFFERENT DOSES OF MORPHINE IN CLINICAL GROUPS C, D, AND E

Patient Classification	Clinical Group	Dose of Morphine (mg.)	No. of Tests	Grade of Change					
				0	1a	1b	2	3	4
Controls and no encephalopathy	C	8	12	11	0	0	1	0	0
Certain encephalopathy	E	8	34	4	3	9	8	4	6
Doubtful encephalopathy	D	8	32	4	10	7	7	3	1
Controls and no encephalopathy	C	16	9	4	1	1	3	0	0

be seen that irrespective of dose and clinical grouping (not shown on this figure) the general effect of morphine is to produce a reduction in dominant frequency and an increase in RAO, considered as indices of EEG deterioration. No particular significance may be attached to the relative positions of the 8 mg. and 16 mg. points since the larger dose was given to less severely affected patients and was discontinued during the investigation.

Table II contrasts the grade of change produced by different doses given to different clinical groups. It refers to tests and not to patients. The four grade 0 tests in group E patients were repeated under different conditions and gave positive responses. The one test in group C graded 2 was on a patient with a peptic ulcer who at the time was being treated with phenobarbitone, grain 1½ t.d.s., and it may be that the effect of the large dose of phenobarbitone and the small dose of morphine was comparable to that of 16 mg. of morphine. The results in this table show that patients in group E responded more vigorously to 8 mg. of morphine than do those in group C; that this differential effect is quantitative not absolute, because some patients in group C show a response to the larger dose; some patients in group E may, under certain conditions, show a grade 0 response, although under other conditions they show a greater one; and the division into grades is arbitrary and there are many points in the grade 0 area of Fig. 2 which show an appreciable reduction in frequency and increase in RAO.

On the whole patients in group D show a response intermediate between those in groups C and E. This is the group in which a diagnostic test is required and although a large response would be very suggestive of encephalopathy a smaller one would be equivocal.

The dose of 16 mg. was stopped during the investigation, first, because of the poor differentiation between groups C and E, and secondly, because some group E patients showed a very marked EEG response to this dose. Although they were not affected clinically it was felt that the larger dose

TABLE III

Clinical Group	Patient No.	Differential Morphine Tests			Grade	Diet, Treatment, and Additive Morphine Tests			Grade
		Records Compared	Numerical Change			Records Compared	Numerical Change		
			Dominant Frequency	% RAO			Dominant Frequency	% RAO	
E	1	P..Pm	− 27	+ 7	0	P..Q	− 14	− 27	0
	1	Q..Qm	—	—	4	—	—	—	—
E	8	P..Pm	− 87	+ 13	1b	—	—	—	—
	8	Q..Qm	− 183	+ 62	3	—	—	—	—
E	13	P..Pm	− 50	+ 25	2	P..Q	− 41	+ 62	1a
	13	Q..Qm	—	—	4	—	—	—	—
E	33	R..Rm	+ 2	+ 38	1a	—	—	—	—
	33	S..Sm	− 100	+ 42	2	—	—	—	—
E	36	Q..Qm	desynchronized		0	—	—	—	—
	36	S..Sm	− 108	+ 35	2	—	—	—	—
E	40	P..Pm	− 41	− 11	0	P..R	− 49	+ 28	1a
	40	R..R	+ 36	+ 2	0	—	—	—	—
	40	R..Rm	− 126	+ 61	2	P..Rm	− 175	+ 105	3
E	41	P..Pm	—	+ 2	4	P..Q	− 56	− 19	1b
	41	Q..Qm	—	+ 56	4	—	—	—	—
E	43	P..Pm	− 124	+ 6	1b	P..Q	− 83	− 50	1b
	43	Q..Qm	− 123	+ 250	2	P..Qm	− 206	+ 75	3
E	44	P..Pm	− 150	+ 49	3	P..R	− 177	+ 80	3
	44	R..Rm	—	—	4	—	—	—	—
E	52	P..Pm	− 56	− 2	1b	P..Q	+ 69	+ 12	0
	52	Q..Qm	− 251	+ 58	3	P..Qm	− 182	+ 78	3
C	51	R..Rm	desynchronized		0	R..S	desynchronized		0
	51	S..Sm	desynchronized		0	R..Sm	desynchronized		0
	51	T..Tm	desynchronized		0	R..T, R..Tm	desynchronized		0

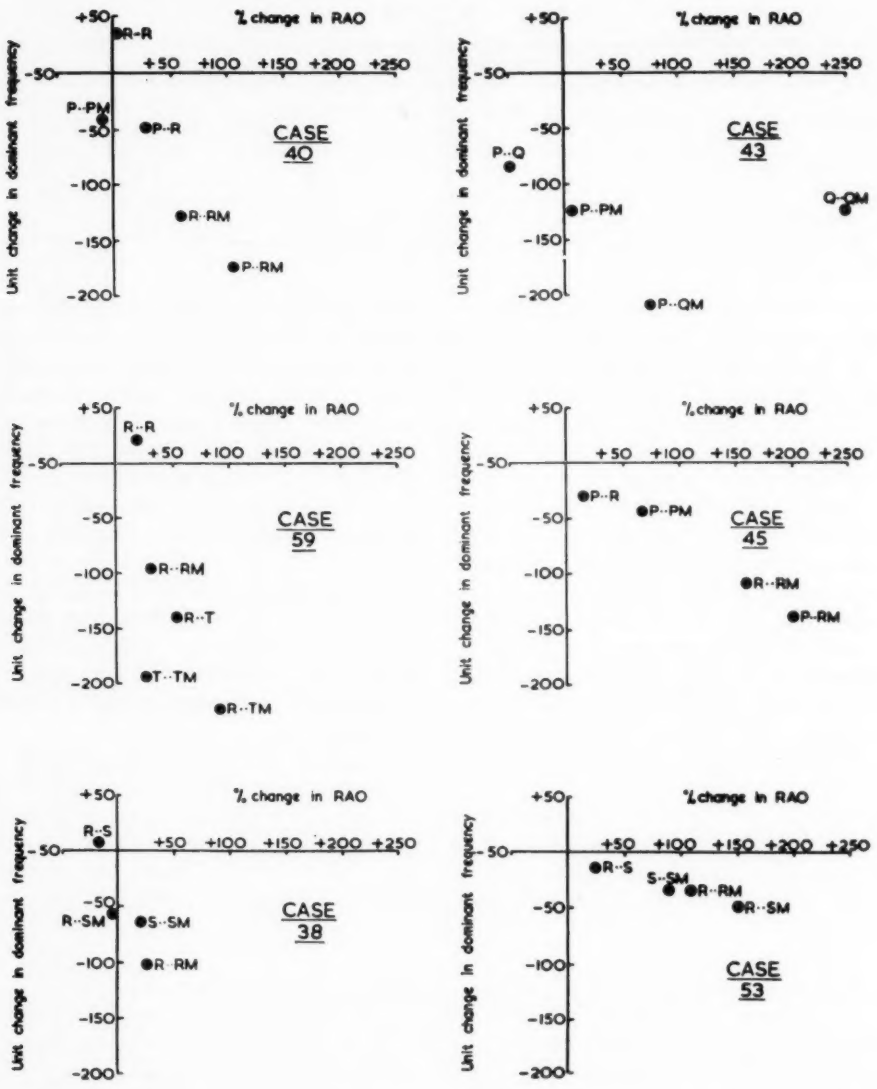

FIG. 3.—Graphic representation, similar to that in Fig. 2, of deterioration in EEG as a result of morphine and changes in diet and treatment (see also Tables III and IV). Cases 40 and 43, clinical group E; Cases 59, 45, 38, and 53 group D. The EEG tests support the diagnosis of hepatic encephalopathy in Cases 59 and 45, are against it in Case 38, and provide some evidence in favour in Case 53.

might be dangerous. The test dose of 8 mg. proved harmless in the 66 tests on group D and E patients.

From the results so far presented it may be postulated that the EEG response to morphine is related to the presence and to the degree of encephalopathy. Alterations in diet or treatment (conditions P, Q, R, S, or T) affect encephalopathy. If the above hypothesis is correct, such alterations should produce a differential response to morphine. The left side of Table III shows the results of these differential morphine tests in 11 patients, 10 from group E and one from group C, expressed in grades of change, and, except for desynchronized records and those showing grade 4 change, numerically. Each group E patient showed a positive differential test, a greater response on going from P to Q to R to S. Ammonium chloride was not given to these patients. The one patient in group C showed no such change. The results for patients 40 and 43 are shown graphically in Fig. 3. A dummy morphine test, R-R, is shown for patient 40.

In some patients with hepatic encephalopathy EEG deterioration may be produced by diet changes alone. The effect which, like the response to mor-

TABLE IV

Clinical Group	Patient No.	Differential Morphine Tests				Diet, Treatment, and Additive Morphine Tests			
		Records Compared	Numerical Change		Grade	Records Compared	Numerical Change		Grade
			Dominant Frequency	% RAO			Dominant Frequency	% RAO	
D	38	R..Rm	− 101	+ 24	1b	R..S	+ 8	− 19	0
	38	S..Sm	− 65	+ 18	1b	R..Sm	− 57	− 5	1b
D	45	P..Pm	− 44	+ 67	1a	P..R	− 30	+ 15	0
	45	R..Rm	− 109	+ 160	2	P..Rm	− 139	+ 200	2
D	47(i)	R..R	0	+ 3	0	—	—	—	—
		R..Rm	− 132	+ 104	2	R..S	− 3	0	0
		S..Sm	− 64	+ 7	1b	R..Sm	67	+ 7	1b
	47(ii)	R..Rm	− 119	+ 81	2	R..T	− 45	+ 104	1a
		T..Tm	− 144	− 17	1b	R..Tm	− 189	+ 69	3
D	49	R..Rm	− 2	− 8	0	R..S	+ 22	+ 39	1a
	49	S..Sm	− 66	+ 12	1b	R..Sm	− 44	+ 56	1a
	49	T..Tm	− 103	+ 16	1b	R..T	− 26	+ 53	1a
	—	—	—	—	—	R..Tm	− 129	+ 73	2
D	50	Q..Qm	− 36	+ 26	1a	Q..S	− 16	+ 5	0
	50	S..Sm	− 108	+ 27	2	Q..Sm	− 124	+ 33	2
	50	T..Tm	—	—	4	Q..T	− 48	+ 48	1a
D	53	R..Rm	− 34	+ 119	1a	R..S	− 15	+ 24	0
	53	S..Sm	− 34	+ 90	1a	R..Sm	− 49	+ 150	1a
D	59	R..R	+ 21	+ 17	0	—	—	—	—
	59	R..Rm	− 95	+ 30	2	R..T	− 138	+ 51	2
	59	T..Tm	− 194	+ 26	3	R..Tm	− 233	+ 91	3

phine, consists of a fall in dominant frequency and percentage increase in RAO, is shown to the right of Table III. The comparison has not been made for patients 8 or 33 since the two morphine tests were several weeks apart, or for patient 36 since the Q record contained too little rhythmic activity for numerical assessment. Since the diet and morphine changes are measured in the same units they can be added and the results, the additive morphine test, are also shown to the right of Table III. If EEG deterioration is produced both by morphine and change of diet the additive test will of course be positive. Its value lies in demonstrating a significant change when the changes produced by the single tests are too small to be considered diagnostic, and like the differential test in making it possible to attribute a non-specific sensitivity to morphine (or encephalopathy) to liver disease.

These differential and additive results in patients in whom the diagnosis is known first support the hypothesis that the response to morphine and encephalopathy are related, and, secondly, suggest that when the diagnosis is in doubt these additional tests may enable a firm EEG diagnosis to be made. In such milder cases the results from the simple morphine test or from the diet alone may be equivocal. Table IV shows full results for seven patients in group D and these will be considered in more detail.

Case 38 (Fig. 3).—The small changes R..Rm and S..Sm show a more than usual sensitivity to morphine. However, there is no R..S change and the differential and additive morphine tests are both negative. The EEG evidence does not favour the diagnosis of hepatic encephalopathy.

Case 45 (Fig. 3).—The P..R effect is very small and, alone, is not convincing. P..Pm, although bigger, is also insufficient for a definite diagnosis. However, the diagnosis of hepatic encephalopathy is strongly supported by the positive differential morphine test (R..Rm is greater than P...Pm) and the additive test (P..Rm) which is greater still.

Case 47.—This is a difficult case and the tests were repeated. In the first series when normal diet was contrasted with a high-protein one, there is evidence for encephalopathy since both the morphine tests are positive and the dummy morphine test shows considerable inter-record stability, but there is no deterioration on a high-protein diet alone and the differential and additive tests are negative, thus arguing that the encephalopathy is not hepatic. In the second series ammonium chloride, a stronger provocative agent, was used, and produced some deterioration alone (R..T) and a positive additive test (R..Tm) although an equivocal differential test. On the whole the EEG evidence is in favour of hepatic encephalopathy. It is of interest to note the similarity of the R..Rm changes in the two series.

Case 49.—This is of interest as there was a negative morphine test on normal diet (R..Rm) but a good differential morphine effect progressively from high-protein diet to ammonium chloride. There are small R..S and R..T effects and so a good additive morphine test. There is good evidence for hepatic encephalopathy but this is very mild and only likely to produce delirium under considerable provocation.

Case 50.—All three morphine tests are positive with strong differential effects. High-protein feeding produces a very slight and negligible deterioration (Q..S) but ammonium chloride is more effective (Q..T). The additive morphine effect (Q..Tm) is irrelevant since T..Tm has already shown a maximum change. There is strong evidence in favour of hepatic encephalopathy.

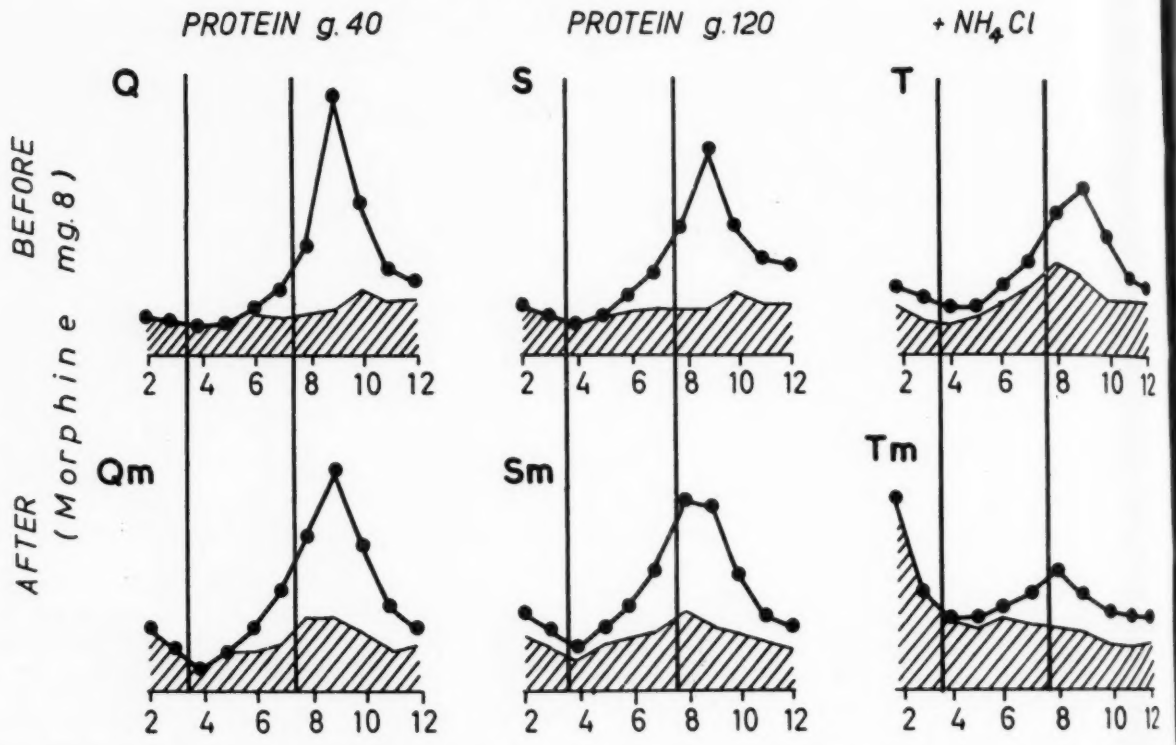

FIG. 4.—Case 50. Six frequency patterns of rhythmic activity with eyes shut (● — ●) and with the eyes open (shaded), before and after morphine under different conditions of diet and treatment (see also Table IV).

This case is illustrated (Fig. 4) in the form of frequency patterns.

Case 53 (Fig. 3).—All the changes are very small. Both morphine tests are positive; the differential test is just negative. Although the effect of a high-protein diet (R . . S) is graded 0 there is some change as shown numerically, and, therefore, a positive additive test. The patient may have very mild hepatic encephalopathy.

Case 59 (Fig. 3).—There are two positive morphine tests, no change in the dummy morphine test, a good differential response, and considerable deterioration on ammonium chloride which produces a marked additive morphine effect. There is good evidence for the diagnosis of hepatic encephalopathy.

Discussion

Simple psychological tests to assess minimal confusion were given at the time of most EEG recordings. These showed good general correlation with the EEG responses to morphine but suggested that the latter were rather more sensitive and reliable. These results will be reported elsewhere (Cang and Laidlaw, in preparation). The clinical problems of the diagnosis of confusion complicating liver disease have been stated very briefly and rather dogmatically and may appear to gastroenterologists to have been oversimplified. This aspect of the work will also be dealt with elsewhere (Read *et al.*, in preparation), and it is sufficient to say that the EEG methods described have proved of real clinical value.

A very great deal of EEG work has been done on localized and paroxysmal abnormalities whereas relatively little attention has been paid to the clinical applications of the study of the background rhythmic activity, whether normal or abnormal. There seem to be two main reasons for this neglect.

1. Localized or paroxysmal abnormalities, if likely to have clinical significance, are usually clearly apparent in the primary EEG record, whereas the background activity is usually in the form of complex rhythms which are much more difficult to appreciate or assess.

2. It is comparatively simple to determine whether a localized or an episodic change is significant since they may be contrasted either in space or in time with what is normal or usual for a particular patient. On the other hand the background activity of a single record may only be considered as abnormal if it differs significantly from the background rhythms of large numbers of controls. Since the normal range is very wide indeed, significance

can only be attached to gross variations and the EEG detection of such changes is seldom likely to provide information which could not have been obtained by clinical methods. However, under a number of circumstances, the background rhythmic activity varies with alterations in brain function, and the measurement of changes in this activity for an individual may provide an index of brain metabolism which is more sensitive than clinical examination or psychological testing.

If, therefore, the background activity of the EEG is to yield clinically valuable information, it is necessary in the first place to have a simple and valid method of reducing complex rhythms to a form which can readily be appreciated and compared, and, in the second place, to determine under what circumstances these measures of change in background activity may be considered as indicative of altered cerebral function and not merely as a manifestation of random fluctuation.

The theoretical aspects of different types of analysis have been fully reviewed (Burch, 1959; Kozhevnikov, 1958). Obrist and Henry (1958) carried out a careful comparison of visual and electronic methods and found that both gave essentially similar results, except that like Burch and ourselves they concluded that automatic analysis gave dubious results at low frequencies. We are satisfied that the type of analyser we have used is suitable. It is simple, relatively cheap, requires little adjustment, and is quite sufficiently accurate for ordinary clinical work.

The choice and arrangement of epochs was that found by experience to be the most satisfactory. There must be enough epochs to allow assessment of interepoch variability but the recording must be short enough to anticipate possible deterioration in the patient's condition, since it is very important that any two records being compared should have the same number and arrangement of epochs. The alteration of S, O, and L epochs at the beginning of the recording is intended to prevent too much relaxation and may be contrasted with the effect of the three consecutive S epochs at the end. The Lc epoch is put at the end for convenience in changing the light pattern. Immediately after shutting the eyes many people show transient faster rhythms (Storm van Leeuwen and Bekkering, 1958) but in normal subjects the rhythms tend to stabilize quickly and a satisfactory reading is obtained by analysing from 15 to 30 seconds after shutting the eyes. The O and L epochs were also taken this time after opening the eyes since the amount of return of rhythmic activity under alerting conditions is a more sensitive index of delirium than the immediate blocking effect of opening the eyes.

A simple adaptation to the analyser allows the activity at individual frequencies to be written out alongside the original record and this is considered valuable. It provides a useful visual check on meter readings, enables change to be assessed in records containing little rhythmic activity, and demonstrates interesting intra-epoch frequency fluctuations. The appearance of high-amplitude delta waves sufficient to dominate the record represents a severe abnormality which can be recognized readily without recourse to electronic frequency analysis and for most purposes no reliance need be placed on the rather unreliable meter readings for very low frequencies.

Detailed numerical comparison between records is based on values calculated for dominant frequency and rhythmic activity under different conditions. In the large series of morphine tests only two measures of deterioration were used, namely, reduction in units of dominant frequency and percentage increase in RAO. This limitation was made first because these values were available for tests throughout the series; secondly, because previous work (Laidlaw, 1959; Read *et al.*, 1959) showed that these changes were found consistently during the early stages of developing delirium; and, thirdly, because more complicated methods of comparison would have yielded no additional useful information. However, in small series or when single pairs of records are being compared a more sophisticated comparison may be useful. Experience has suggested that the following points may be important:

1. The amount of random change from one record to another has been found to vary between patients and to be related to the amount of interepoch variation for that patient. If, therefore, a subject shows little interepoch fluctuation, significance can be attached to smaller inter-record changes.

2. In some subjects there is a tendency for the amount of rhythmic activity with the eyes shut (RAS) to vary from one epoch to another inversely with dominant frequency. In such subjects changes in dominant frequency to be considered significant should be greater than those to be expected from concomitant change in RAS. It may be noted here that with increasing delirium there is a general tendency with fall in dominant frequency for RAS either to remain unchanged or to increase, whereas when a subject becomes drowsy it is usual for dominant frequency and RAS to fall together.

3. RAL and RALc are less subject to spontaneous fluctuations than RAO and in some cases an increase in these values provides a more reliable index of deterioration. However, in other cases

looking at or counting light patterns produces so much blocking of rhythmic activity that the index is too insensitive.

Measurements are made not of the background activity of a single record but of the difference in such activity between records and are expressed as a degree of deterioration, comparison always being made in the direction in which deterioration may be expected to occur. This method is based on the premise that each individual has, subject to random fluctuations, an optimum or usual record with his own usual values for dominant frequency, RAO, etc., and that factors which produce a general interference with brain metabolism cause the same type of EEG deterioration, namely, reduction in dominant frequency and increase in rhythmic activity under alerting conditions. In as far as these factors are reversible when they are corrected there will be a return to the usual level but over-correction will not produce a supra-optimum record. Previous work (Read *et al.*, 1959) showed that hypokalaemia was one such factor. Low levels of serum potassium might produce a slowing of dominant frequency, restitution to normal would correct this slowing, but hyperkalaemia never produced a level of dominant frequency higher than was usual for the subject. Efron and Kent (1957) suggested that there was an optimum value for carbon dioxide tension and that any marked change, whether an increase or a decrease, produced a reduction in the frequency of the cerebral rhythms. For a patient with known or suspected encephalopathy we do not know whether or not the values for frequency and activity in a resting record represent his pre-morbid optimum. However, the record made under the most favourable circumstances is most likely to approximate to the usual level and should be used as the baseline for comparison whether or not it was the first recorded. It is for this reason that all comparisons in Tables III and IV are made in the direction from P to Q to R to S to T.

For a measured difference between two records to be considered as indicative of an alteration in brain function it is necessary that it should be greater than that which might occur as a result of random fluctuation. It has been our experience that some patients with encephalopathy show greater fluctuations than normal subjects, fluctuations which if not random are due to causes unknown. It is not, therefore, altogether satisfactory to consider as significant in patients changes which are outside the limits of those found in controls. It is considered better, as in the series described, to contrast the changes between different groups or between records in the same patient under different conditions. When comparing a large number of pairs of records in a big series some form of grading is convenient but it will inevitably be relatively coarse as a measure of change. In that which we have used the limits have been set widely so that it would be improbable for a change graded other than 0 to be due to random fluctuation, but the converse is not true, and some of those changes graded as 0, particularly in subjects showing little interepoch variation, may have been due to altered brain function. In small series or when individual pairs of records are being compared it is recommended that arbitrary grades should not be used but that change between records should be considered as significant if appreciably greater than the individual interepoch change or the inter-record change under conditions when no deterioration could be expected. Thus patients 47 and 59 (Table IV) showed a certain inter-record change R..R during dummy morphine tests. The changes R..Rm may be considered significant in contrast to these changes.

The system described may be used as a diagnostic tool. A patient suffering from an acute general interference with brain function which we have termed 'delirium' is likely even in the very early stages to show EEG deterioration. Even if his record lies within the normal range, it will show values for dominant frequency, etc., below his individual optimum. At this stage, when there is often no convincing clinical evidence, the diagnosis both of delirium and of its cause may be made by a therapeutic test in which EEGs are compared after and before some measure intended to correct the presumptive cause of the delirium. Thus perhaps a patient with hepatic cirrhosis is confused and it might be thought that this is due to liver disease. His EEG (R) is classified as normal. He is given neomycin and the EEG is repeated after three days (P). The second record may also be classified as normal but there is a difference between the records and this shows deterioration from P..R, suggesting that record R did not represent his usual record, providing EEG evidence of delirium, and specifying the cause of the delirium as something amenable to treatment with neomycin, making the presumptive diagnosis of hepatic encephalopathy.

In many cases, however, what is required is a measure of a chronic latent tendency to develop episodes of delirium, what we have termed encephalopathy. In severe cases a resting EEG may lie below the patient's optimum and there may be room for the therapeutic test. However, in the milder cases, which present the diagnostic problems, the resting record is likely to be at or near the patient's usual level (the encephalopathy is not only clinically but electrically latent), and it is in these cases that the use of the type of provocative tests

which have been described may prove very valuable. We have described the use of non-specific provocations, such as morphine, added to specific provocations, such as increasing the protein in the diet or adding ammonium chloride. There are cases when a non-specific provocation may give a more or less specific diagnosis because of the clinical context. Thus, a marked EEG deterioration with a small dose of morphine in a patient with hepatic cirrhosis, possibly suffering from encephalopathy, provides good evidence not only of encephalopathy but of hepatic encephalopathy. The specific forms of provocation are usually less effective but they may be reinforced by combination with a non-specific provocateur as in the additive morphine test or they may enable significance to be attached to equivocal results from non-specific provocation as in the differential morphine tests.

The general principle underlying the use of provocative tests may be illustrated diagrammatically (Fig. 5) where each circle represents an EEG, the letters written beside having the same meaning as in the clinical investigation reported above, and the distance apart of the circles representing the amount of change from one record to another. Since ER..ERm and ES..ESm are greater than CR..CRm and CS..CSm patient E suffers from greater brain sensitivity to provocative agent 'm' than control C, *i.e.*, suffers from encephalopathy. Since ER..ES is greater than CR..CS and since ES..ESm is greater than ER..ERm, this encephalopathy is due to a disorder made worse by the provocation represented by the change of condition from R to S.

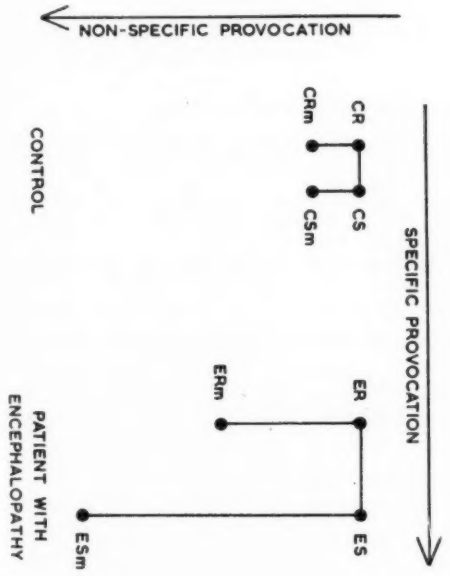

FIG. 5.—Schematic diagram to contrast the effect of provocation (m) on patients without encephalopathy (C) with those with encephalopathy (E) under different conditions (R and S) such that the direction of expected deterioration is from R to S. m = non-specific provocation, R-S = specific provocation

It is suggested that the system of analysis which we have described provides a satisfactory method of measuring changes in the background rhythmic activity of the EEG and enables the significance of these changes to be assessed, and that the production of such EEG changes by appropriate therapeutic or provocative tests may provide a useful diagnostic tool applicable to a variety of conditions in which the metabolism is disordered of those deeply placed structures of the brain, which, it is presumed, play an important part in the control of EEG rhythms and the maintenance of a normal level of consciousness.

Summary

A method, based on electronic analysis, of assessing the background rhythmic activity of the electroencephalogram is described. The difficulties in obtaining useful information about this activity from a single record are emphasized and a system of quantitative measurement of change between records is described.

Episodes of confusion or alteration of consciousness are defined as 'delirium' and the tendency to develop such episodes as 'encephalopathy'. The EEG is very sensitive to the onset of delirium and the criteria of EEG deterioration along the continuum from normal consciousness to coma are defined.

Certain patients with hepatic cirrhosis may be said to suffer from hepatic encephalopathy in that they are liable to develop episodes of delirium. The application of this EEG method to the diagnosis and assessment of hepatic encephalopathy is described in some detail in order to demonstrate its clinical usefulness.

Patients with mild encephalopathy may show no clinical or EEG abnormalities. In these cases the EEG changes of delirium may be provoked by appropriate measures often without clinical change and at no risk to the patient.

The measurement of change in background rhythmic activity, the significance of such change, and the production of changes by therapeutic and non-specific and specific provocative tests are discussed.

We wish to acknowledge the support and advice of Professor Sheila Sherlock under whose care were the patients described, and to thank the Medical Research Council for personal grants, and Miss R. Harrison, chief dietician, and Miss A. Lees, electroencephalographer.

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THE NOVEMBER (1960) ISSUE

The November (1960) issue contains the following papers:—

Nerve Fibre Degeneration in the Brain in Amyotrophic Lateral Sclerosis. Marion C. Smith

The Distribution of Lewy Bodies in the Central and Autonomic Nervous Systems in Idiopathic Paralysis Agitans. W. A. den Hartog Jager and J. Bethlem

The Effect of Haemodialysis in Myasthenia Gravis. Ernst Stricker, Heinrich Thölen, Marie-Agnes Massini, and Hans Staub

Traumatic Epilepsy after Closed Head Injuries. W. Bryan Jennett and Walpole Lewin

A Myopathy Presenting in Adult Life with Features Suggestive of Glycogen Storage Disease. J. MacDonald Holmes, C. R. Houghton, and A. L. Woolf

Changes in Nerve Conduction with Ulnar Lesions at the Elbow. R. W. Gilliatt and P. K. Thomas

The Clinical Significance of the Sinu-Vertebral Nerve of the Cervical Spine in Relation to the Cervical Disk Syndrome. Ralph B. Cloward

An Experimental Analysis of Confabulation in a Case of Korsakoff's Syndrome using a Tachistoscopic Method. Maria Wyke and Elizabeth Warrington

The Effect of Focal Lesions of the Brain upon Auditory and Visual Recent Memory in Man. Lucjan Stepień and Stanisław Sierpiński

5-Hydroxyindoles in Mental Deficiency. C. M. B. Pare, M. Sandler, and R. S. Stacey

Society of British Neurological Surgeons: 61st Meeting

Book Reviews

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J. Neurol. Neurosurg. Psychiat., 1961, **24**, 71.

THE RIGID FORM OF HUNTINGTON'S DISEASE

BY

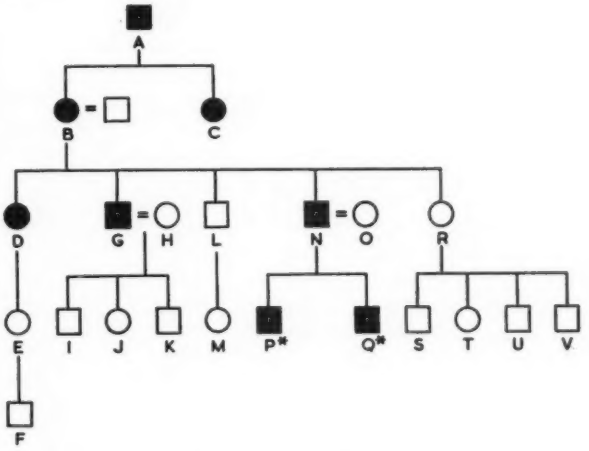
A. M. G. CAMPBELL, BERYL CORNER, R. M. NORMAN, and H. URICH

From the Department of Neurosurgery and Child Health, Bristol Royal Hospital, and the Burden Neuropathological Laboratory, Frenchay Hospital, Bristol

Although the majority of cases of hereditary chorea correspond accurately to the classical pattern described by Huntington (1872), a number of atypical forms have been recorded in children and adults which are characterized by rigidity rather than by hyperkinesia. Most of these have been reported in the continental literature and we thought it was of interest to draw attention to two atypical juvenile cases occurring in an English family.

From Reisner's (1944) review of these juvenile cases the fact emerges that although the majority present with typical choreiform movements, two atypical variants also occur: one in which the clinical picture is that of progressive extrapyramidal rigidity without involuntary movements, the other in which the disease starts as a hyperkinetic syndrome and gradually changes into a hypokinetic one with progressive rigidity. These two syndromes are commoner in the juvenile group, though occasional similar cases have been recorded in adults, in some instances affecting entire families, like that of Schob (1927), in which rigidity followed a preliminary stage of chorea, and that of Hallervorden (1957), in which rigidity was the predominant symptom throughout the course of the illness. Finally, there is the unusual case briefly recorded by Westphal (1905). This patient came from a family with seven other members affected by Huntington's chorea. Choreic movements in this patient developed late in the course of the disease, mental abnormality having been observed for 12 years, and Parkinsonian rigidity and intention tremor having been present for seven years before the onset of typical hyperkinesia. No post-mortem findings were described.

Clinical accounts of these atypical variants, both juvenile and adult, are fairly numerous (see Hallervorden, 1957) but detailed pathological studies are rare. The classical description of juvenile cases which never exhibited choreiform movements is that of Spielmeyer (1920, 1926) who described two cases recorded clinically (as instances of Wilson's disease) by Kraepelin (1921) and shown by the genetic study of Entres (1925) to belong to a typical Huntington family. More recent contributions are those of Rotter (1932), Hempel (1938), and Lindenberg (1960). Bielschowsky (1922) gave a detailed account of the pathological findings in a patient who was choreic at the age of 6 years and from the age of 9 gradually developed Parkinsonian rigidity. Our own juvenile case is remarkable in



Family tree made in December, 1956.

A A Died in a mental hospital.
B Mrs. C. Died in a mental hospital, aged 45, in 1922.
C Died in a mental hospital.
D Mrs. S. Died in a mental hospital, aged 50.
E Mrs. F.
F R.F. Aged 18 months.
G HH. Now in a mental hospital. (Onset of first symptoms 40-43 years.)
H N.H. Now in hospital with rheumatic arthritis and "heart trouble".
I V.H. Married.
J.K., P.H., and J.H. Have recently been medically examined and are apparently free from the disease.
L H. Died of pneumonia in hospital, aged 26.
M Stillborn.
N B.H. Now in a mental hospital. (Onset of first symptoms 38-40 years.)
O No information available.
P* B.H. Died in a hospital, September, 1956, aged 18.
Q* J.H. Aged 16, the patient, onset aged 12.
R Mrs. K.
S, T, V A.K. 17, M.K. 14, C.K. 8.
U Stillborn.

that mild choreic movements became established after the Parkinsonism had been present for about seven years. This sequence of events thus resembles that in Westphal's case.

The family we have studied lived in Bristol but had relatives who were traced back to Scottish ancestry and Cornwall. The older members of the family do not concern us in this paper, but two of them have been seen by one of us (A.M.G.C.) numbered G. and N. in the family tree. These were classical cases of Huntington's chorea presenting with mental symptoms and choreiform movements at the age of about 40. Both had been apparently normal during the earlier years of their life and able to hold reasonable jobs until the onset of the disease. Both are now confined to a mental hospital. Case N. had two sons who form the basis of this particular paper. The following is the case history of the first boy who was under the care of one of us (B.C.).

Case Reports

B.H., the first child in this family, was seen at the age of 10 years 2 months on account of severe attacks of asthma which began during his third year. A very undersized child with the weight and body measurements of a boy of only 7 years, he had severe pulmonary emphysema, consolidation of the left lower lobe, and antral sinusitis, for which he was admitted to hospital for investigation.

It was then observed that he was a very shy, immature boy, who made no attempt to play or converse with other children in the ward. The striking features were his expressionless face and generalized rigidity. No involuntary movements were observed. Hand movements were so poorly coordinated that he was unable to wash or dress himself, and he fed himself with obvious difficulty and very messily. His voice was low pitched and articulation poor. On questioning, his mother admitted that she had noticed increasing stiffness of his legs and difficulty in walking for about a year. A diagnosis of Parkinsonism, possibly post-encephalitic, was made.

During the next two years his physical condition steadily deteriorated. Generalized rigidity and shuffling gait increased, a fine tremor developed, and he became almost inarticulate. All deep reflexes and abdominal reflexes were brisk, and plantar responses flexor. No sensory changes were elicited. Treatment with artane was tried without effect.

No abnormality was seen in the cerebrospinal fluid.

Air encephalography showed in the lateral ventricles slight dilatation, in the left greater than in the right.

No alpha activity was detected in the E.E.G., but diffuse delta and theta waves from all areas.

The Wassermann and Kahn reactions were negative. The blood group was A Rh positive, the blood count normal, and plasma proteins normal.

Thymol turbidity was 4 units, thymol flocculation partial, colloidal gold flocculation 2 units, and plasma phosphatase 14 units.

Urinary copper and amino-acid excretion was within normal limits.

His I. Q. (Terman Merrill) was 76, and arithmetic ability was grossly retarded.

Two years and nine months after he was first seen his paternal aunt died in hospital having been diagnosed as a possible case of Huntington's chorea, and his father was in hospital with the same condition. Shortly after this, at 13 years of age, the boy had two severe major fits, and three months later typical choreiform movements developed in the left hand. He also complained of persistent itching of the dorsum of both feet. During the next two months the fine tremor greatly increased and there were also continuous choreiform movements in both legs and arms. He was still attending a day school for physically handicapped children but with frequent absences owing to asthma.

At the age of 15 years he was again admitted to hospital as the fits had now become very severe and occurred almost daily. Mentally he was cooperative and slightly euphoric, but responsive within the limits of his motor disability. He was still able to read, and was interested in his surroundings.

During the subsequent months there was very rapid deterioration in his physical and mental state so that shortly before his sixteenth birthday he was admitted to a hospital for the chronic sick, bedridden, with advanced pseudo-bulbar palsy and severe mental deterioration. An E.E.G. at this time showed generalized abnormality as before. He died at the age of 17 years 11 months.

The second boy, J.H., case Q, closely resembled his brother in his clinical features. At the age of 14 the mother noticed that the boy began to get slow and clumsy in his movements. His mother also noticed that he had a tendency to fall; the mother was, of course, aware at this time of the family history and of the brother's illness, and she was on the look-out for the development of symptoms in this particular boy. He apparently had quite a good school record, was not brilliant but not noticeably backward. He left school at the age of 15 and worked in a mattress factory.

Recently he has found that he is unable to carry the heavy loads he could manage formerly. On examination it was noticed that he had an immobile facial expression and that he had marked rigidity resembling the rigidity of Parkinsonism. He moved with difficulty and slowly, his speech was slightly slurred, and coordination of movements was impaired. He also showed generalized extrapyramidal cogwheel rigidity throughout all four limbs. His gait was stiff and there was a marked tendency not to swing his arms, particularly the left one.

This boy has gradually deteriorated over the three years he has been under observation, although it is obvious that he is not unintelligent, but unfortunately he has an insight into the possible future development of his disease in a similar way to that of his brother. During the last year of observation a certain number of involuntary movements have become obvious in the left hand, but rigidity still dominates the picture and when he

was shown at a clinical meeting about 18 months ago, without the family history being divulged, the majority of clinicians decided he must be a case of post-encephalitic Parkinsonism.

The interest, therefore, of these two cases is, first, the precocious development of the disease in these two boys compared with the course in their ancestors who developed the disease at a much later age, and secondly, the development of rigidity as a predominant feature rather than involuntary movements or mental changes.

Examination of the Central Nervous System in Case 1

Macroscopic.—The fixed brain weighed 1,172 g., the cerebellum and brain-stem accounting for 178 g. The convolutional pattern was normal but the sulci were widened over the convexity of the cerebral hemispheres, particularly so in the central region and in the occipital lobes. On coronal section the lateral ventricles were markedly dilated in symmetrical fashion and severe atrophy was seen in the caudate nuclei and putamina (Fig. 1). The globus pallidus of each side was also shrunken but relatively less so than the striata. The blood vessels and meninges were unremarkable.

Microscopic.—Large representative blocks of the cerebral hemispheres, basal ganglia, cerebellum, and brain-stem were embedded in celloidin and sections stained for nerve cells and myelin. Frozen sections were stained for myelin, nerve cells, lipid, and fibrous neuroglia. On the right side the basal ganglia were examined at millimetre levels from the mammillary bodies to the terminal part of the globus pallidus. On the left side, hemisphere sections were similarly examined from the middle of the nucleus sub-thalamicus to the posterior termination of the external geniculate body.

Cerebral Cortex.—Both postcentral gyri were severely shrunken and showed a substantial and diffuse loss of nerve cells mainly in the third and fifth layers (Fig. 2). In the precentral gyrus similar neuronal losses were more patchily distributed, the giant cells of Betz being well preserved but crowded together. A generalized reduction in the depth of the cortex was commonly seen (Figs. 3a, 3b). In places the two lowest layers of the motor cortex were the most affected. Nerve cells were widely destroyed in both occipital lobes, mainly in the smaller cells of the third layer but often diffusely, as in the parastriate cortex (Fig. 4). In the visual cortex changes were less intense and the deeper part of the internal granular layer was usually the best preserved in the more affected gyri. In much of the prefrontal, parietal, and temporal areas the architecture of the cortex was well preserved though patchy areas of nerve cell loss were common and many of the nerve cell bodies appeared slightly shrunken. A selective degeneration of extensive parts of the internal granular layer was frequently seen in the temporal isocortex. The hippocampal formations were intact. No lipid granules or excess of lipochrome were seen in the nerve cells. The supraradial myelinated fibres were scanty in the better preserved gyri and in the atrophied regions the radial fibres were also feebly represented. The destruction of nerve cells was not associated with fibrillary gliosis except in the molecular layer and to a less extent in the outer part of the grey matter. The centrum ovale and the medullary cores of many gyri were markedly reduced in volume. In general, no demyelination was demonstrated in frozen sections, though in celloidin-embedded material the staining of myelin was often not so intense as in normal brains. In the atrophied occipital and central regions the white matter showed a mild, diffuse, fibrillary gliosis and a few fat granule cells were occasionally seen around vessels.

Basal Ganglia.—Both striate bodies were grossly atrophied, the caudate nuclei being represented by an elongated thin strip of tissue and the putamina severely shrunken to about one-third of the normal size (Fig. 1). The small nerve cells had virtually disappeared while many of the larger ones had survived and were crowded together (Fig. 5). There was a marked increase of glial nuclei throughout the whole striatum but a fibrillary gliosis was demonstrated only in the putamen (Fig. 6). The strio-pallidal fibre bundles were thin, rather poorly myelinated, and showed an apparent increase of oligodendroglia.

The globus pallidus was also shrunken, its area in cross section being about half that of normal. In the anterior part of the nucleus the nerve cells appeared healthy though more closely packed together than in the normal adult. There was a marked increase in oligodendroglial nuclei (Fig. 7a). Myelination was not reduced and no pallor or gliosis was seen in the position of the "strio-nigral tract". More posteriorly the pallidal fibres stained poorly in myelin preparations and areas could be found in the external segment in which the nerve cells were less numerous and individually very small and poor in Nissl substance (Fig. 7b). Fibrillary gliosis was marked in the posterior part of the nucleus. The divisions of the ansa lenticularis were identified and appeared normal except for slightly reduced intensity of myelin staining.

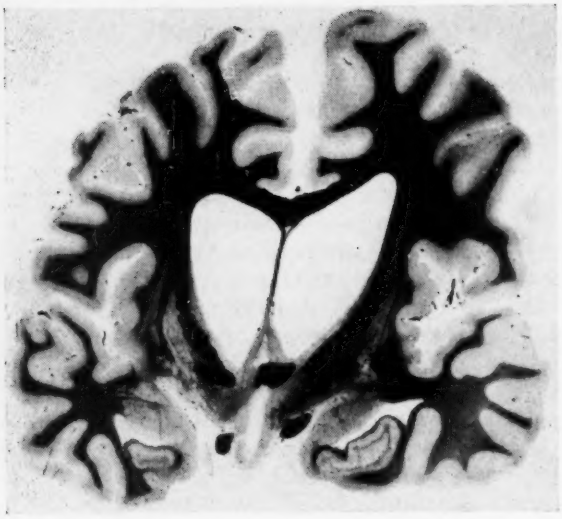


FIG. 1.—Coronal section through the frontal lobes showing marked atrophy of the centrum ovale, caudate nuclei, and putamina. Heidenhain × 0·8.

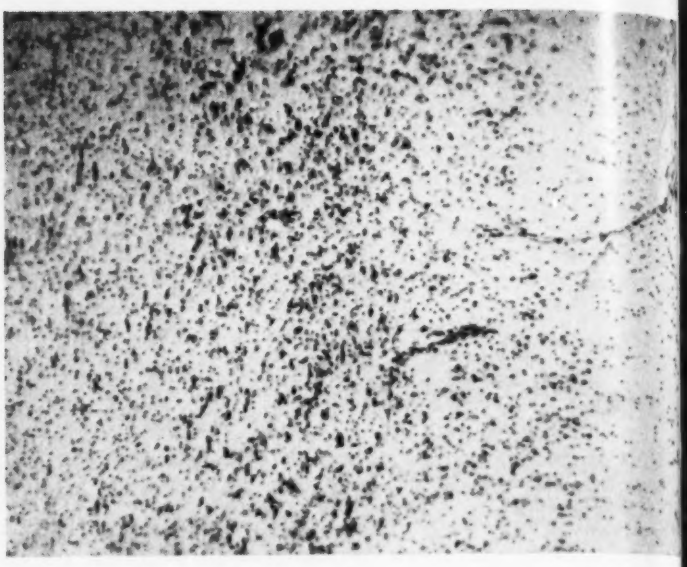
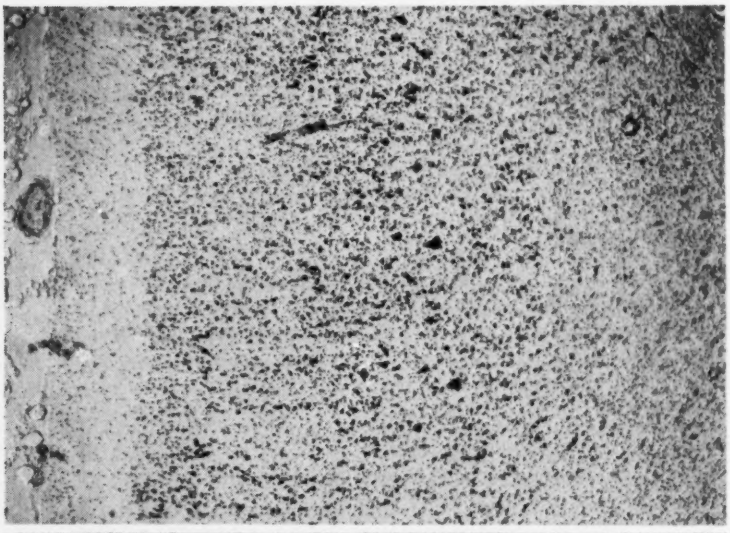
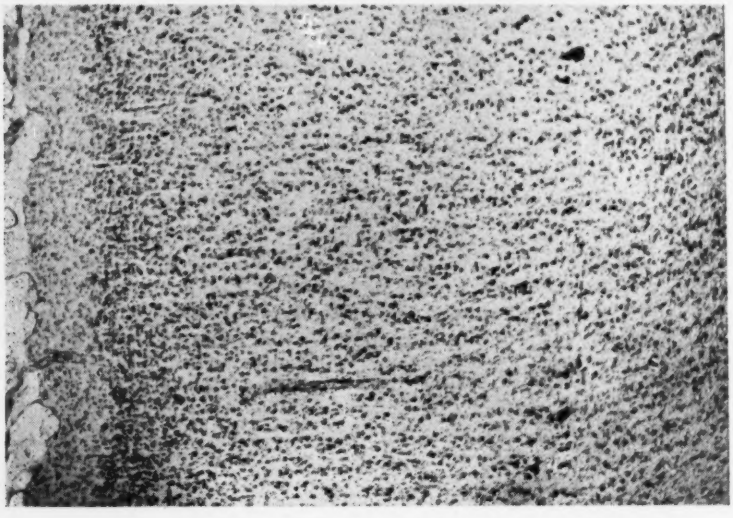


FIG. 2.—Postcentral gyrus showing diffuse degeneration of nerve cells. Carbol azure × 80.



a



b

FIG. 3a.—Precentral gyrus showing generalized reduction in the depth of the grey matter. 3b.—Normal control. Carbol azure × 40.

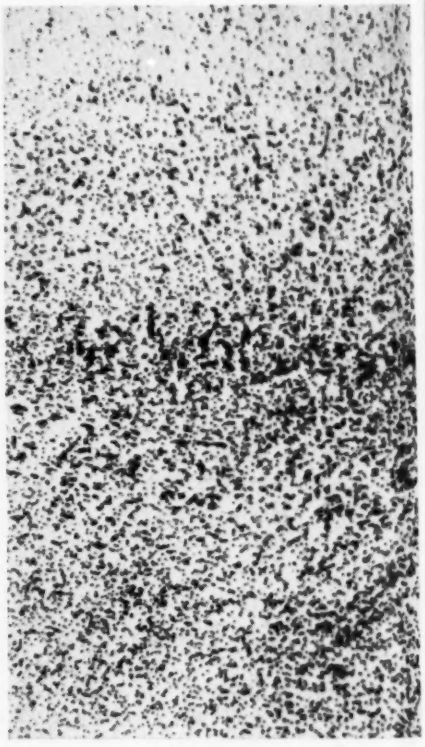


FIG. 4.—Parastriate cortex showing severe degeneration. The large nerve cells of the lower part of L3 are relatively preserved. Carbol azure × 75.

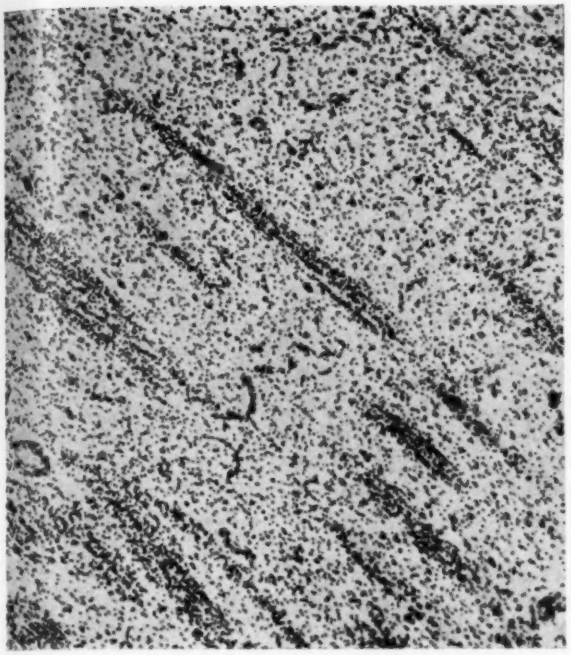


FIG. 5.—Putamen. The small nerve cells are almost completely lost. The astrocytic nuclei are increased in number. The striopallidal fibre bundles are crowded together and show an excess of oligodendroglial nuclei. Carbol azure × 60.

FIG. 6.—Fibrillary gliosis in the putamen and posterior part of the globus pallidus. Holzer × 3.

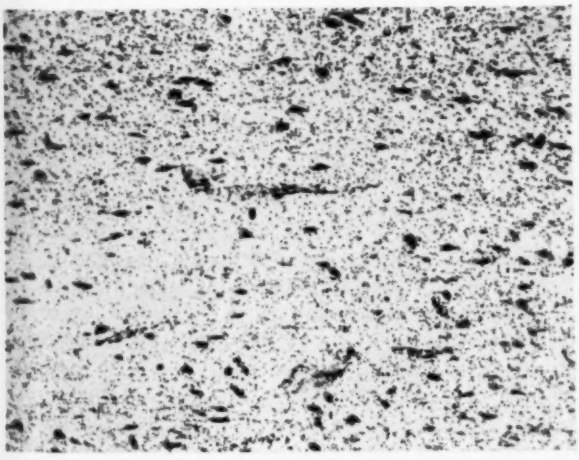


FIG. 7a.—Globus pallidus, anterior level. The nerve cells are normal in appearance but are unduly crowded together. Carbol azure × 60.

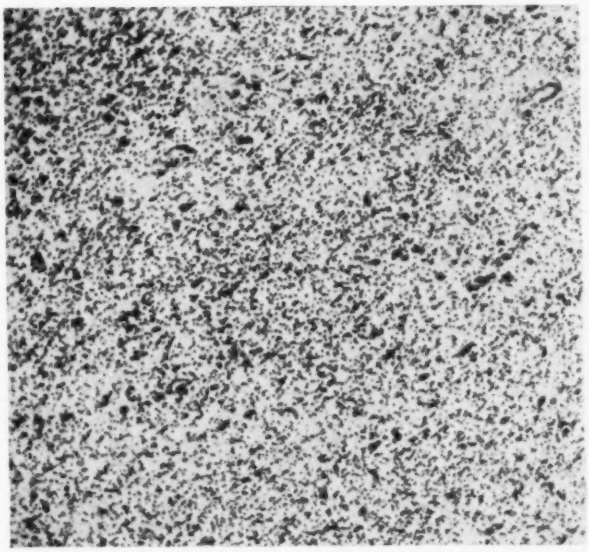


FIG. 7b.—Globus pallidus, posterior level. There is a reduction in the numbers of nerve cells, many of which are shrunken. Carbol azure × 60.

The claustrum and amygdaloid nucleus were intact.

The thalamus appeared somewhat flattened laterally in coronal sections but no significant loss of nerve cells was found in the various nuclei. Detailed examination of the corpora Luysii revealed no lesion.

The lateral lobes of the cerebellum, vermis, and dentate nuclei were normal.

Brain-stem.—Although no loss of nerve cells could be demonstrated in the substantia nigra the neurones generally appeared smaller and contained less melanin pigment than those of the normal adult. The cell groups as a whole had shrunk a little and the cytons appeared rather crowded together. The red zone was markedly narrow and in places contained an excess of glial nuclei. The red nucleus appeared to be normal. The cerebellar peduncles and other tracts and nuclei were unaffected. The pons appeared normal except for marked gliosis and a slight loss of nerve cells in the superior olives.

No pathological changes were seen in the medulla. In the spinal cord there was a distinct pallor of myelin staining in the peripheral zone of the anterior cord lateral columns throughout the cord. The nerve cells were unremarkable.

Discussion

Attempts to distinguish pathologically between the choreic and akinetic forms of Huntington's disease have not revealed clear-cut differences despite the striking clinical contrast. Bielschowsky's (1922) conclusion that the rigidity of his patients could be ascribed to the severity of the pallidal lesions was contraverted by Spielmeyer (1926) who pointed out that the pallidal changes in his own rigid cases were less marked than those often found in purely choreic patients. In certain instances pallidal lesions have been found in combination with degeneration of the large striatal nerve cells (Jakob, 1923) but the latter feature is not usually seen in the akinetic type of the disease and cannot be regarded as a significant factor in the production of rigidity.

In the light of recent neurosurgical experience and from the results of animal experiments this simple correlation of pallidal lesions with rigidity must be dismissed as obsolete. Yet it is well to bear in mind that the beneficial effects of pallidectomy on hyperkinesia depend upon relatively minor pallidal damage, only about 10% of the whole nucleus being involved (Carpenter, Whittier, and Mettler, 1950). One cannot safely assume that very extensive pallidal destruction is similarly innocuous, otherwise the crippling disabilities of kernicterus and progressive pallidal degeneration (van Bogaert, 1946) would be inexplicable. In Huntington's disease, however, this consideration does not apply, for the pallidum may be relatively spared both in the choreic and akinetic forms.

Later authors who have compared the two variants from the pathological point of view have been impressed by the more massive character of the lesions in the rigid cases, though they have found that the same structures may be involved in both forms. Not only are the striatal lesions very severe and diffuse but there is usually a marked generalized cerebral atrophy with considerable ventricular dilatation and brain weights below 1,000 g. (Meyjes, 1931; Rotter, 1932; Hempel, 1938). There is thus a substantial, though ill-defined, cortical component in the syndrome. In our case the brain weighed 1,172 g. so that the atrophy of the centrum ovale was evidently less than may occur in the akinetic cases. On the other hand, the severity of the nerve cell loss in the caudate nucleus and putamen was fully equivalent to what has been described in all the rigid cases. The solution of the problem awaits the quantitative assessment of the damage suffered by the various nuclei concerned in the regulation of involuntary movement and muscle tone, and this is a task of great difficulty. An estimate can, however, be made on the basis of serial sections and certain findings in the present cases, particularly the integrity of the corpus Luysi and substantia nigra, appear worthy of comment when set against the background of Purdon Martin's (1959, 1960) recent analysis of basal ganglia function.

In the first place the Parkinsonian rigidity in our case was not associated with a loss of nerve cells in the compact zone of the substantia nigra. This is also true of other juvenile rigid types of Huntington's disease described in the literature. A rare striopallidal-nigral syndrome, also characterized by rigidity, has been reported by Vander Eecken, Adams, and van Bogaert (1960) but this appears to be a distinct pathological entity and its genetic relationship to Huntington's chorea not yet established. If, then, the rigidity in our case was due to the overaction of the pallidum, that is to say, by the operation of the "supplementary tone-producing mechanism" suggested by Martin, the release of excessive pallidal activity must have been due to lesions in a centre or centres other than the substantia nigra. Although the globus pallidus was shrunken the nerve cells were largely preserved, especially in the medial segment, and the divisions of the ansa were intact. There were also no detectable lesions in the thalamus. It would thus appear that an essential

mechanism for the production of rigidity (or hyperkinesia) had been relatively preserved. It may be suggested, though it cannot be proved, that this release of pallidal activity may have been conditioned by the severe degeneration of the putamen. As Martin (1959) has pointed out, "not all extrapyramidal rigidity is associated with significant disease of the substantia nigra. Wilson's disease provides the best example of the contrary and . . . in this condition the striatum suffers severely". This statement is in harmony with the views expressed by Denny-Brown (1960) on the causation of rigidity in Huntington's disease in his recent Croonian lectures. In a personal communication he writes: "The essential point is that rigidity ensues when the inner part of the putamen becomes seriously damaged". A corollary to this hypothesis would be that early and severe degeneration of the putamen may be responsible for the purely akinetic varient of the disease. It may be of significance that in our case a dense fibrillary gliosis was present in the putaminal part of the striatum and not in the caudate nucleus.

The second point of interest raised by this case concerns the appearance of mild choreic movements late in the course of the patient's illness. Evidently the structures responsible for this manifestation had not been destroyed or their action permanently suppressed by the lesions causing the initial state of rigidity. Important findings were the complete escape of the bodies of Luys and of the dentato-rubral system. There remain the lesions of the caudate nuclei and the cerebral cortex as sources of that functional upset in the balance of power which seem to underlie choretic movements. The experiments of Kennard and Fulton (1942) have shown that in the chimpanzee true unilateral chorea followed combined extirpation of cortical area 6 and the caudate nucleus of the opposite side. The findings in our case were not so clear cut, for although there was no doubt as to the severity of the caudate nuclear degeneration, the prefrontal region merely shared the generalized cortical atrophy and was not preferentially involved. It seems advisable, however, to admit the possibility of a cortical component in the hyperkinesia of Huntington's disease, since the evidence favouring purely striatal lesions as a cause of chorea is controversial (Meyers, 1942).

. We therefore suggest that the choreic and akinetic types of Huntington's disease owe their contrasting clinical features to the relative severity of the caudate-cortical degeneration on the one hand and of the putaminal degeneration on the other. The temporal sequence of these lesions must also have a decisive influence on the clinical picture.

Summary

Details have been given of an English family in which classical Huntington's chorea has been traced for three generations. In the fourth generation two brothers suffered from the juvenile, rigid form of the disease. In the elder a Parkinsonian rigidity began at about the age of 10 years. At the age of 13 this patient began to have major epileptic fits and choreiform movements in the limbs appeared for the first time. He died bedridden and with advanced pseudo-bulbar palsy at the age of 17 years. Neuropathological examination showed widespread cerebral cortical atrophy with maximal involvement of the postcentral gyri and the occipital lobes. The centrum ovale was atrophied and the lateral ventricles considerably enlarged. Severe symmetrical atrophy affected the caudate nuclei and putamina from which the small nerve cells had largely disappeared. The globus pallidus was shrunken but there was little loss of nerve cells except in the external segment. The compact zone of the substantia nigra was normal except for slight general shrinkage. No lesions were found in the corposa Luysii or dentato-rubral system. It is suggested that the akinetic form of Huntington's disease is primarily characterized by the severity of the putaminal lesions, while the choreic manifestations of this disorder are due to involvement of the caudate nuclei, perhaps in association with their cerebral cortical connexions.

We are much indebted to Dr. Purdon Martin for his advice on many problems arising during the preparation of this paper. The neuropathological part of this work was assisted by the Nuffield Foundation.

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RESPONSE OF NORMAL AND MULTIPLE SCLEROTIC SUBJECTS TO TYPHOID-PARATYPHOID VACCINE INJECTIONS

BY

E. J. FIELD, C. A. GREEN, and HENRY MILLER

From the Royal Victoria Infirmary, Newcastle upon Tyne and the Prudhoe and Monkton Hospital, Prudhoe, Northumberland

The suspicion that an immune reaction is involved at some stage in the pathogenesis of multiple sclerosis is implicit in much of the recent literature of the disease (Miller and Schapira, 1959). If this were so, multiple sclerotic subjects might possibly manifest an enhanced capacity to produce antibodies; or alternatively, if they are actively producing auto-antibodies, then their capacity to respond to other antigens might be diminished.

To explore these possibilities the responses of multiple sclerotic patients to the inoculation of a standard typhoid-paratyphoid vaccine (T.A.B.T., Burroughs-Wellcome) have been evaluated and compared with those in normal subjects.

Method

In this series 21 multiple sclerotics and 23 control subjects were examined. The latter were physically healthy high-grade mental defectives, actively employed, and taken to represent 'normal controls'. The patients with multiple sclerosis were in various stages of the disease but no apparent differences were noted in the responses obtained.

In each case a Widal test was carried out before the first injection to serve as a 'base-line', after which 0·5 ml. T.A.B.T. No. 1 (Wellcome) was injected into the deltoid muscle of the non-dominant arm. This No. 1 antigen is a vaccine comprising heat-killed organisms as follows:—

S. typhi 500
S. paratyphi A 250 } million organisms in 1 ml.
S. paratyphi B 250

The first few multiple sclerosis patients were confined to bed for 48 hours after inoculation and their temperatures recorded four-hourly, but in the absence of any constitutional reactions this procedure was soon abandoned.

At the end of 14 days another Widal test was performed and a second intramuscular injection of antigen given, this time 1 ml. of T.A.B.T. No. 2 (Wellcome). This No. 2 antigen also comprises heat-killed organisms, but in the following amounts:—

S. typhi 1,000
S. paratyphi A 500 } million organisms in 1 ml.
S. paratyphi B 500

A month later, *i.e.*, six weeks after the initial injection, the Widal test was repeated and a further 1·0 ml. T.A.B.T. No. 2 injected. Care was taken to use the same batches of T.A.B.T. No. 1 and 2 for groups of controls and patients.

This procedure of Widal test followed by a further 1·0 ml. T.A.B.T. No. 2 injection was repeated monthly for six to eight months.

To meet the possibility that a short-lived response to injection might disappear within a month, and be missed when the next Widal test was done, a subsidiary experiment was carried out in which Widal tests were done one week (and sometimes again two weeks) after inoculation with T.A.B.T. No. 2. Eight multiple sclerosis patients and 15 controls were investigated in this way. The results of this series are set out in Table I.

No therapeutic effect was noted amongst the multiple sclerotic patients, though one or two reported temporary subjective improvement. On the other hand no untoward effects were observed in either the control or the experimental group.

The Widal test (or more strictly the 'tube agglutination test') as carried out routinely in this hospital was used throughout. The antigen employed was that supplied by the Standards Laboratory of the Public Health Laboratory Service. The range of serum dilutions was 1 : 25, 1 : 50, 1 : 125, 1 : 250, 1 : 500, 1 : 1,000, 1 : 2,500, 1 : 5,000, 1 : 10,000, 1 : 20,000, 1 : 50,000, and 1 : 100,000. Incubation was carried out in a water-bath for four hours at 50°C., the tubes being stored overnight and read the next morning after having remained at room temperature for 30 minutes.

Results

In assessing the results of the short-term experiment presented in Table I, only a difference of titre of at least two tubes in the Widal test has been accepted as significant, since a rise of one tube may possibly fall within the range of experimental error. The cases listed had no demonstrable TO antibodies before the relevant injection, so the elevations shown are from a zero base-line. Since all these subjects had been previously injected several times at monthly intervals, it is a secondary

TABLE I
RESPONSES ONE WEEK AFTER RE-INOCULATION WITH T.A.B.T. No. 2

No. of Tubes Showing Increase in Titre			
Controls		Mutiple Sclerosis	
E.A.H.	—	R.G.	—
L.A.H.	3	B.S.	—
J.Q.	3	A.L.	—
T.M.	—	P.S.	—
T.H.	2	E.M.	—
E.K.	6	E.F.	—
G.W.S.	—	E.D.	—
D.P.	3	E.J.F.	—
R.H.	3		
S.B.	—		
E.W.B.	3		
G.F.L.	—		
E.B.	2		
E.J.P.	—		
G.D.	3		

If a two-tube rise from the zero base-line is accepted as certainly positive, then x^2 (with Yates' correction) = 4·518 and P = 0·02. There is less than one chance in 500 that this difference is coincidental.

response which is being assessed. Under these conditions analysis shows a significantly greater response by control subjects than by multiple sclerosis cases. The changes in BO agglutinins were not significant, nor were those in any of the other titres which were examined.

The long-term experiments indicated that the difference between control and multiple sclerosis cases noted above was a transient phenomenon, and that in both groups repeated monthly inoculations produced a variable and uniformly ill-sustained response in all O titres.

To the question propounded in the introduction to this paper it seems possible to give a definite answer. Established cases of multiple sclerosis show a diminished immediate TO response as compared with normal subjects. On the other hand no differences are found during a subsequent period of six months or more. The incidental finding that normal subjects manifest only a moderate response, which may level off or prove poorly sustained, was unexpected after such intensive administration of vaccine.

(Considerations of space prevent the publication of detailed protocols. Records of antibody responses extending in some cases up to 10 months are available and would be gladly supplied to anyone wishing for detailed information.)

Discussion

The main object of this study was to investigate the immune response in multiple sclerosis, and from this point of view it would appear that sufferers from this disease react less vigorously to TO antigen than do control cases. The significance of this empirical finding will be evident only when information is available about the response encountered in patients with other nervous disorders causing comparable grades of 'debility': no difference related to the degree of disablement was noted in the present study.

Of four sisters, E.B., E.J.P., E.M., and P.S., E.B. and P.S. are uniovular twins. P.S. and E.M. suffer respectively from advanced and mild multiple sclerosis. Neither of the multiple sclerotic sisters nor the normal sister E.J.P. responded to TO antigen at one week, but E.B., the unaffected identical twin of the advanced case, responded normally. This finding does not suggest a familial tendency to react unusually, but further experiments, preferably employing the response to immunization against tetanus, might furnish further information on this point.

Surprisingly, no long-term observations of the kind we have made appear to have been reported. Failure of somatic antibodies to appear after prophylactic T.A.B. vaccination has been recorded by a number of workers (Stuart and Krikorian, 1928; Felix, 1924; Gardner, 1929).

Isolated tests made some time after vaccination have, however, suggested that responses were not very well sustained (Wilson, 1945).

The absence of any prolonged boosting effect was an unexpected finding, which re-opens once more the issue of the efficacy of routine T.A.B.T. prophylaxis, recently also called into question by the careful field studies of Cvjetnović (1957). For historical reasons this method of protection has never been subjected to controlled trial, and personal enquiry amongst those best qualified to judge reveals considerable scepticism as to its practical value.

Summary

Multiple sclerotic patients produce less TO antibodies in response to a booster inoculation of T.A.B.T. No. 2 (Wellcome) than do control subjects.

Neither multiple sclerotic patients nor controls show a sustained O response, even when monthly injections are repeated on eight occasions.

We should like to thank Dr. G. McCoull, O.B.E., Prudhoe and Monkton Hospital, and Dr. T. H. Bates, Hunter's Moor Hospital, for their cooperation in making suitable subjects available for this investigation. The assistance of the technical staff of the Department of Bacteriology, and in particular of Mr. E. C. Elliott, F.I.M.L.T., is also gratefully acknowledged.

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A HUGE OSTEOMA IN THE ANTERIOR CRANIAL FOSSA

BY

VI. HUDOLIN, D. RIESSNER, S. KADRNKA, and M. KNEŽEVIĆ

From Neurolosko-Psihijatrijski Odjel, Zagreb

Osteomata with intracranial complications are rare, so that even today they attract interest (Campbell and Gottschalk, 1938; Hariga, 1960), especially when they are not arising from the paranasal sinuses, where they usually originate.

Recently we had occasion to observe a patient with an osteoma of unusual size situated in the anterior cranial fossa. The clinical picture was that of a case of frontal lobe syndrome with personality changes and symptomatic epilepsy. We are describing the case because of the unusual site of the osteoma and also as a contribution to the diagnosis of the psychiatric syndrome in lesions of the frontal lobe.

Osteomata in the intracranial cavity must be distinguished from secondary bone formations and from the so-called osteoplastic meningiomata (Cushing, 1937). According to the medical literature they are very rare, and are usually found either as small bony formations of the cranium, or as exostoses in the region of the anterior clinoid processes, the lesser wings of the sphenoid bone, or pyramidal portion of the temporal bone (*porus acusticus internus*) (Lindgren, 1954; Ritvo, 1949; Coley, 1949). Osteomata in these sites show very little tendency to grow. More frequently osteomata are found in the paranasal sinuses or arising from the orbital roof, and these orbitoethmoidal forms can lead to complications following their penetration into the intracranial cavity. Frontal lobe complications in the cases hitherto described arose after penetration of the accompanying mucocele into the intracranial cavity then into the brain substance and finally into the ventricles (Cushing, 1927; Campbell and Gottschalk, 1938; Hariga, 1960). Spontaneous pneumocephalus and meningitis are the complications usually described. Peters (1951) mentions that oesteomata of the cranium are relatively rare and gives Courville's classification, namely, 1, circumscribed osteoma of the cranial vault (single or multiple); 2, diffuse osteoma (usually arising from the great wing of the sphenoid or from the temporal bone); 3, osteoma of the orbito-ethmoidal region; and 4, osteochondroma arising from the base of the skull.

Cushing (quoted by Zülch and Christensen, 1956) had in his series of 2,023 tumours only 14 osteomata. Zülch and Christensen (1956) in their own 4,000 cases of cerebral tumour mention 16 osteomata, while Olivecrona (quoted by Zülch and Christensen, 1956) had no cases of osteoma in his series of 5,250 cases.

The frontal lobe syndrome presents a psychiatric clinical picture which although well recognized cannot be accurately localized or aetiologically determined by clinical methods. When this syndrome has existed for some considerable time, and when there is also severe damage to the frontal lobe, the question then arises whether restoration of mental faculties is in any degree possible, especially when the patient has only psychiatric symptoms which do not allow of accurate objective measurement because the personality changes resulting from frontal lobe lesions cannot be satisfactorily measured by the usual psychological tests. Frontal lobe tumours are usually found in patients in mental hospitals since they very often present only psychiatric symptoms uncharacteristic of any definite clinical picture.

Case Report

A peasant woman aged 57, living in the neighbourhood of Zagreb, was admitted to the Neuropsychiatric Department as an emergency case. At the time of admission no details of her illness could be obtained because of her severe mental derangement and poor physical condition. According to the statement of her husband there was no family history of neuropsychiatric relevance. Since 1937 she had suffered from epileptic fits. She had been prone to drink heavily since early youth, and especially since the end of the Second World War. She had already received hospital treatment in 1954 having been treated as a chronic alcoholic with antabus. Shortly after hospital treatment she suffered from an extremely severe attack of epilepsy, being unconscious for one hour followed by a disturbed mental state for several days. Visual hallucinations were

present. She was again admitted to a mental hospital and discharged after 18 days as a case of chronic alcoholism with symptomatic epilepsy; she was treated with anticonvulsant drugs.

Her husband remarked that after discharge from hospital on this second occasion she was 'a changed person'. She was restless, forgetful, and careless in her behaviour. Her condition slowly deteriorated, her epileptic attacks occurred once every two or three months, but she did not take anticonvulsants regularly. She continued to drink heavily.

Three months before her admission to our hospital she began to complain of 'terrible headaches' and after a particularly severe headache she lapsed into coma and was admitted to the provincial hospital where she was diagnosed as a case of apoplexy. She was comatose for the first three days after admission. At the end of 12 days she was sufficiently recovered to be allowed home, at the request of her family and against medical advice and before neuropsychiatric investigations had been done. From that time her mental state rapidly deteriorated. She was confused, she spoke at times about herself disconnectedly, saying that it would be better to keep quiet but that she had to speak, etc. At this time she was eating little and drinking heavily and she lost a great deal of weight. Finally, she was admitted to our hospital. On admission she was incontinent of urine and faeces. She responded to questioning, but quite irrationally. She thought that she was in her native village school. She would not change her opinion about this in spite of it being pointed out to her that she was surrounded by hospital beds and not by school desks. She could not grasp who the people around her were. She showed no spontaneous interest in her surroundings, but smiled constantly in a good humoured manner. She offered no resistance to medical or nursing care and was indifferent to injections. She gave the impression that she had no comprehension of what was going on around her. Occasionally she would join in the conversation of the other patients with irrelevant remarks. Among a great many incorrect statements about herself she would make an occasional correct one. She could understand and carry out simple instructions. She would sometimes reiterate a chance word heard from the conversation of others. She had no complaints of any pain.

Clinical Findings.—She was able to walk by herself, but her gait was unsteady with some dystasia. When brought food, she was able to eat unaided. There was no tenderness of the skull on palpation or percussion. No signs of meningeal irritation were present.

The pupils were slightly contracted, equal in size, not distorted; the reactions to light and accommodation were a little sluggish. It was impossible to ascertain the presence or absence of anosmia because of her mental state.

Sensation and the rest of her neurological state could not be estimated accurately but were apparantly normal. Her psychiatric state suggested that she was a psycho-organic case with frontal lobe syndrome.

Of the investigations carried out, we cite only the abnormal: The E.S.R. was 20/47 (Westergren), and the number of cells in the cerebrospinal fluid was increased (34/3). The aorta showed some degree of atheroma in a chest radiograph. The ocular fundi at first showed no abnormality but just before operation a papilloedema of 1D had developed on the right side.

X-ray Findings in the Skull.—Antero-posterior and lateral views of the skull and frontal and sagittal tomography of the anterior cranial fossa (Figs. 1, 2, 3) showed that the skull was normal in shape and size. An opaque shadow approximately 7 cm. in diameter was seen lying on the lamina cribosa equally on either side of the midline. The density of the shadow suggested a homogeneous calcified circular growth with clearly defined and irregular outlines. The lesion extended from the frontal bone to the sella turcica. There was a projection from the edge of the growth on the right side towards the lateral angle of the right orbit with ill-defined edges.

The internal lamina of the vault was thickened, especially in the frontal area. The caudal part of the posterior wall of the frontal sinus and part of the roof of the right ethmoid sinus were narrowed. The lesser wings of the sphenoid bone were thickened. The sella turcica appeared normal and the dorsum sellae was rarefied.

Pneumoencephalography with 40 ml. of air was done, and showed that the frontal horns of the lateral ventricles were shortened. The central parts of both lateral ventricles were widened and, together with the temporal horns and the narrowed basal cisternae, were displaced backwards. These findings suggested that there was a single multicentric osteomateous tumour, the size of an orange, situated on the base of the anterior cranial fossa lying centrally. The growth had produced backward dislocation of the atrophied frontal lobes, ventricular system, and basal cisternae. There was also erosion of the lamina cribrosa on the right side and of the caudal part of the posterior wall of the frontal sinus, and reactive internal hyperostosis, especially in the frontal bone.

Since the lesion shown on the picture suggested an expansive growth of homogeneous structure the differential diagnosis lay between a calcified olfactory meningioma and an osteoma in the anterior cranial fossa. On the basis of the history and the clinical and radiological findings, we diagnosed the case as a psychiatric frontal lobe syndrome caused by an expansive osteomateous growth in the anterior cranial fossa. It was decided that neurosurgical treatment should be undertaken, especially as signs of raised intracranial pressure were now appearing (papilloedema).

A wide osteoplastic craniotomy was performed by Tönis method. After section of the falx, free access to the base of the anterior cranial fossa was obtained. The dura mater was not tense. After the dura was opened a thick gelatinous mass, which enveloped the tumour to a thickness of 1 cm., began to exude through the opening. Similar gelatinous masses are found in all instances producing stagnation of the cerebrospinal fluid and they contained a great deal of cholesterin. The tumour, which appeared as a white chalky mass, was found to be lying on a broad base on the lamina cribrosa (Fig. 4). It was easy to separate the tumour from the

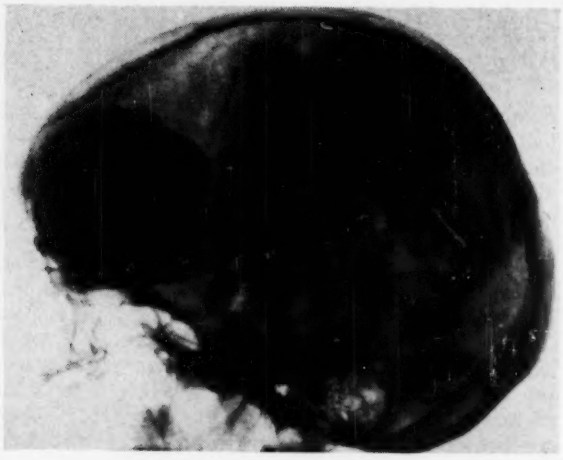

FIG. 1

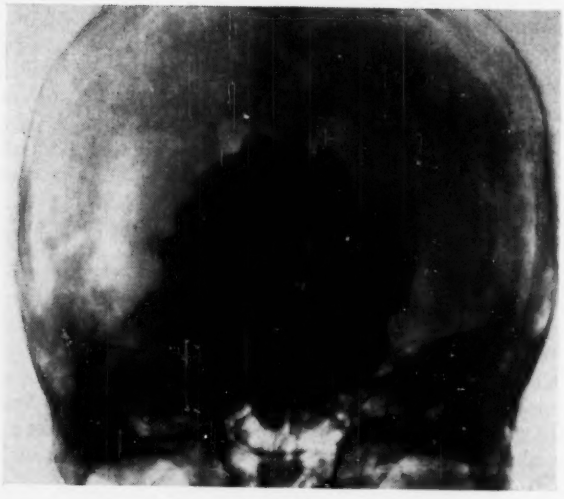

FIG. 2

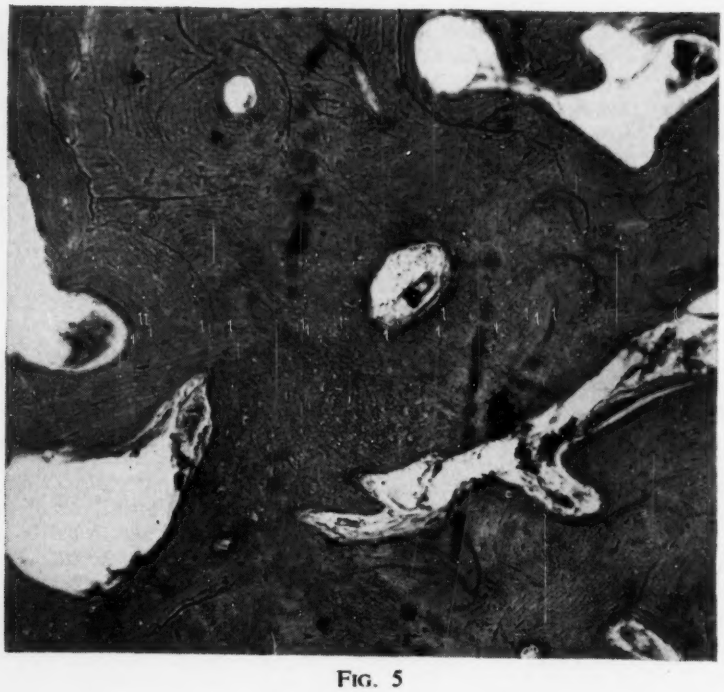

FIG. 5

FIG. 3

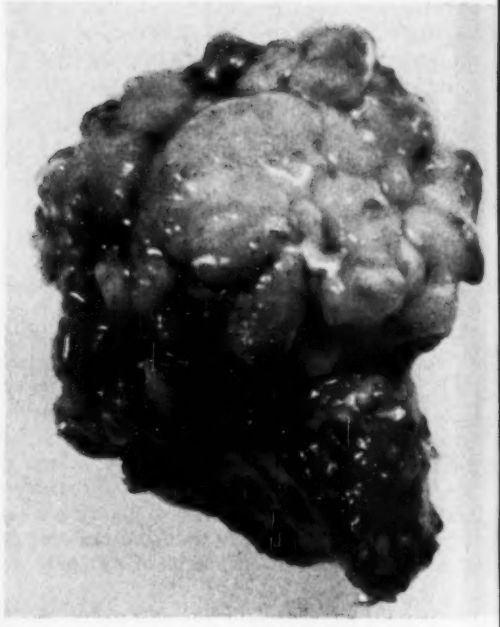

FIG. 4

FIG. 1.—Pneumoencephalogram, lateral view, showing t tumour in the anterior cranial fossa and backward di placement of the ventricular system.

FIG. 2.—Pneumoencephalogram, antero-posterior view, sho ing the tumour centrally placed.

FIG. 3.—Tomogram, lateral view, showing the relation of t central part of the tumour to the floor of the anterior crani fossa. There is no connexion with the paranasal sinuse

FIG. 4.—Tumour after removal.

FIG. 5.—Tumour consisting of thickened bony trabeculae a marrow spaces. × 100.

base of the skull with a chisel. After the removal of the tumour the gelatinous mass was evacuated with a sucker and a large cavity surrounded by the atrophied frontal lobes remained. In the bottom of it the medial formation of the brain was seen. The fact that there were no serious post-operative midbrain reactions was mainly due to the presence of the gelatinous mass which gave relatively easy access to the tumour, and consequently irritation of the midbrain was avoided. The post-operative course was normal.

Pathological Findings.—The tumour was of even consistency on section, and after decalcification it was found to consist of spongy bone tissue containing a small number of normal bone cells and with a normal amount of calcium in the trabeculae. The marrow spaces were narrow without haematopoietic tissue and with fibrous connective tissue and wide blood capillaries (Fig. 5). The tumour compressed the brain substance, producing local necrosis with destruction of the granular cells and an accumulation of crystalline cholesterin. The histological diagnosis was osteoma spongiosum.

After operation the patient's condition quickly improved. She was no longer incontinent, she was well orientated, replied rationally to questions, carried out directions, ate unaided, and even assisted the other patients. She recognized the nurses and recollected that she had seen them before operation, but she could not remember their names. She knew the principal saints days, and remembered all the family facts correctly, and that she had completed the fourth year at the primary school. She was able to do simple arithmetical sums, but quickly became confused if asked to do any more complicated calculation. She read and wrote as well as one could expect for the amount of schooling she had received. She no longer had any delusions or hallucinations. She remembered well events of the distant past, but for recent events of the last few months she had only slight recollection. She had insight into her present condition, she was grateful for her treatment, but there still remained a certain superficiality and lack of responsibility in her behaviour.

Testing olfactory sense, which was impossible before operation, now showed complete anosmia.

After the operation psychological testing revealed no major intellectual deficiency.

Antero-posterior and lateral radiographs taken two-and-a-half months after operation showed that the shadow in the anterior cranial fossa of the previous radiographs was no longer visible. There was a light hyperostosis of the right lesser wing of the sphenoid, and shadows showing the site of the craniotomy.

She was discharged well, and advised to continue to take anticonvulsive drugs although during her stay in hospital she had had no epileptic fits.

Conclusion

This patient had an extremely large osteoma which had slowly developed and escaped diagnosis. From the pathological point of view it was interesting as a rare example of a case where it was possible to decide definitely that the growth was a true osteoma.

The problem of long-standing damage to the cerebral tissue merits special attention. In our case the huge tumour produced almost complete atrophy of the frontal lobes with resultant gross impairment of intellect accompanied by euphoria, personality changes, and alcoholism, all of which had lasted many years. Very soon after operative treatment the clinical picture showed an extraordinary degree of improvement both physical and mental. This case proves the enormous capacity for restoration of function after lesions of the frontal lobes have been removed.

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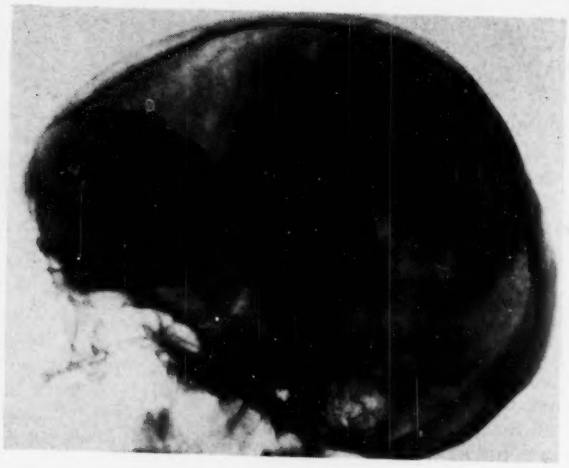

FIG. 1

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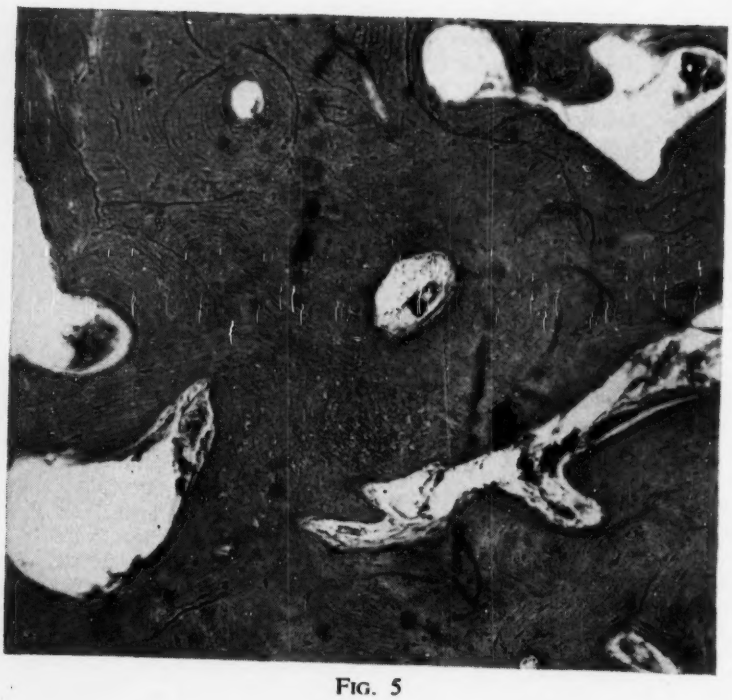

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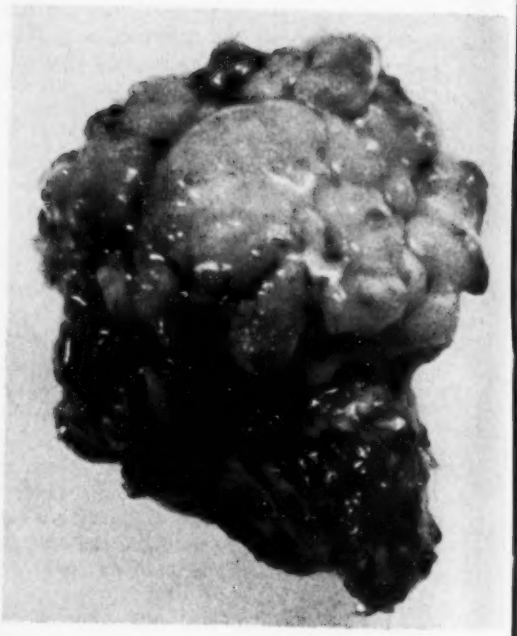

FIG. 4

FIG. 1.—Pneumoencephalogram, lateral view, showing the tumour in the anterior cranial fossa and backward displacement of the ventricular system.

FIG. 2.—Pneumoencephalogram, antero-posterior view, showing the tumour centrally placed.

FIG. 3.—Tomogram, lateral view, showing the relation of the central part of the tumour to the floor of the anterior cranial fossa. There is no connexion with the paranasal sinuses.

FIG. 4.—Tumour after removal.

FIG. 5.—Tumour consisting of thickened bony trabeculae and marrow spaces. × 100.

base of the skull with a chisel. After the removal of the tumour the gelatinous mass was evacuated with a sucker and a large cavity surrounded by the atrophied frontal lobes remained. In the bottom of it the medial formation of the brain was seen. The fact that there were no serious post-operative midbrain reactions was mainly due to the presence of the gelatinous mass which gave relatively easy access to the tumour, and consequently irritation of the midbrain was avoided. The post-operative course was normal.

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AN INTERNAL CAROTID ANEURYSM IN THE PETROUS TEMPORAL BONE

BY

SAMI GUIRGUIS and FATHY W. TADROS

From the Faculty of Medicine, Cairo University

Intracranial aneurysms have received much attention and provoked the interest of many investigators since Biumi of Milan described a case in 1765, a full account of which was later published by Sandifort in 1778.

Out of 559 cases of intracranial aneurysms reported in the literature by von Hofmann (1894), Wichern (1912), Fearnsides (1916), Busse (1920-21), Drennan (1921), Szekely (1928), and Hamby (1952), none was reported to involve the internal carotid artery along its course in the petrous temporal bone.

Pierini and Agra (1954) have described a case of petrous aneurysm without any pathological documentation.

Case Report

The patient, G.D., was a male Egyptian aged 19 years.

History.—Four years before death, the disease started with attacks of left temporal headache, not associated with vomiting. It was partially relieved by analgesics. There was occasional diplopia on looking to the left side. This continued for three years and was followed by the sudden onset of paralysis of the left side of the face. A few months later the patient experienced tinnitus and roaring in the left ear which was followed, in a few weeks, by deafness. Later on, the patient noticed difficulty in swallowing solid food.

There was no ear discharge and no voice changes, or sensory, motor, or visual disturbances.

The patient was a tall, well-built young man with no intellectual or speech disturbances.

Central Nervous System.—Visual acuity was normal and fields of vision were full without fundus changes. The patient had left sixth nerve paresis, lower motor neurone paralysis of the left facial nerve; deafness of the left ear confirmed by audiogram recording; deviation of the soft palate to the right side; weakness of the pharyngeal muscles of the left side, and deviation of the tongue to the left. Coordination was normal. No motor, sensory, or reflex changes were detected.

Examination of the nasopharynx revealed no abnormality. Serological tests were normal.

X-ray Examination.—The left petrous temporal bone showed erosion of the apex of the left pyramid involving the vestibule of the labyrinth.

Operation.—A posterior fossa exploration revealed a soft tissue mass displacing the dura posteriorly over the medial portion of the left petrous temporal bone. The lower cranial nerves were seen piercing the dura and apparently entering the swelling. They looked healthy in their intracranial course. As the dura was being dissected from the swelling a profuse uncontrollable haemorrhage occurred. This necessitated ligature of the left internal carotid artery in the neck, but the patient succumbed shortly afterwards.

Necropsy.—The skull was examined and the left internal carotid artery was followed along its course. Its lumen was probed just before it passed through the carotid foramen (Fig. 1). In its course within the petrous temporal bone it was found to show a marked saccular dilatation which eroded the medial part of the left petrous bone pushing the dura posteriorly where it was pierced by the left lower cranial nerves. The bone, especially at the petrous apex, was found to be rough and eroded, evidently by the pressure of the aneurysmal dilatation. The foramina of exit of the left lower cranial nerves showed irregular spicules of osteophytes.

Swelling and oedema of the left hemisphere were the only naked-eye abnormalities.

Other organs showed generalized acute congestion as a result of medullary failure. No congenital anomaly was noted.

Histology.—The wall of the aneurysm showed thickening of the intima which was formed of fibrous tissue.

FIG. 1.—Photograph of the petrous temporal bone and the internal carotid artery with the aneurysm. A probe is passed through the artery from its entry to its exit, demonstrating the saccular cavity of the aneurysm and the erosion of the bone.

The endothelium was eroded and recent thrombi were adherent to it. The media was replaced by fibrous tissue and only strips of degenerated elastic fibres were noted (Hart's elastic stain and Van Gieson). Sections of bone showed non-specific erosion of the bone constituents, evidently due to pressure atrophy.

Discussion

The clinical diagnosis in this case was difficult. It presented as unilateral multiple cranial nerve lesions in the posterior fossa without any evidence of brain compression and revealed erosion of the petrous temporal bone, features commonly explained by, say, a glomus body tumour. Although most glomus body tumours present with aural symptoms alone, some show both aural and neurological symptoms, and four such cases have been reported (Bickerstaff and Howell, 1953; Revilla, 1948; and Capps, 1952), in which the neurological symptoms were the only manifestation.

All reported cases of glomus body tumour, however, had a much longer history, five to 20 years, compared with the short history in the case reported here.

The clinical picture presented by our case is usually caused by some variety of tumour or occasionally by an aneurysm of the vertebral artery. Our case indicates that a further possibility must be added to the more common causes.

In our case the aneurysm did not occur at an arterial bifurcation. It arose to one side of the stem of the artery. It attained a huge size to reach a diameter of about 4 cm. In structure it is similar to those rare aneurysms seen on the stem of the internal carotid in its intracranial course, the stem of the basilar and that of the vertebral arteries. They usually attain a large size and produce symptoms of compression. The theory accepted for the development of such aneurysms is that they are the result of incomplete involution of an artery or arteries from the original embryonic capillary plexus which develops later in the adult circle of Willis (Sugar, 1951; Padget, 1944; Hamby, 1952).

The nature and histological picture of the reported case suggests that it belongs to this category of aneurysms. It is therefore a true congenital aneurysm which had been present since birth. It had gradually enlarged in size till it eroded the petrous temporal bone and compressed the regional cranial nerves.

Summary and Conclusions

A unique case of aneurysm of the internal carotid artery in the petrous temporal bone is reported; it caused compression of several cranial nerves.

On histopathological grounds this was thought to belong to the category of true congenital aneurysms.

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CHRONIC ARACHNOIDAL CYSTS OF THE MIDDLE CRANIAL FOSSA AND THEIR RELATION TO TRAUMA

BY

P. TIBERIN and J. GRUSZKIEWICZ

From the Department of Neurosurgery of the Rothschild Hadassah Hebrew University Hospital, Jerusalem, Israel

Large accumulations of clear fluid in the cranial cavity, overlying, compressing, displacing, or replacing limited regions of the cerebral hemispheres, are a heterogeneous group of most unusual space-occupying lesions.

According to their apparent location in the subdural or subarachnoid spaces and possible aetiology (focal inflammatory processes, congenital anomalies, trauma of meninges), these fluid-filled cavities or cysts, usually walled off by arachnoidal adhesions, have been described by Abbott (1933), Claude (1933), Okonek (1938), Soule and Whitcomb (1946), Taveras and Rouschoff (1953), and Zehnder (1938) under a variety of terms.

Even though considerable confusion still exists in regard to the location and actual pathogenesis of the arachnoidal cysts, there is general agreement as to the origin of the cystic fluid of which the macro- and microscopic appearances and chemical contents have been found to be quite similar to those of the cerebrospinal fluid. Opinions are also agreed on the potential pressure effects, manifested in particular cases of large collections of fluid, by localized thinning and bulging of the skull, and signs of brain compression.

Although cranial enlargement, together with a subdural accumulation of fluids, was mentioned by Davidoff and Dyke as early as 1938, the first to draw attention to the close relationship that exists between large arachnoidal cysts and the associated localized thinning and bulging of the skull was Childe (1953). The latter author described as 'chronic subdural hygroma' eight such cysts and emphasized their frequent localization in the middle fossa.

This particular type of arachnoidal cyst has, as a rule, a prolonged and relatively benign course, is clinically silent, and usually produces few, if any, symptoms in spite of insidious but progressive enlargement.

As these cysts are most prevalent in children, in whom clinical evaluation is often difficult, their diagnosis is frequently obscure for many months or years and some cases may even escape detection altogether.

At times, because of size and clinical behaviour, they may produce similar effects to those noted with any slowly expanding lesion and the correct nature of the disease process is, therefore, made either at surgery or incidentally at post-mortem examination.

As we have recently had the opportunity to treat a young patient harbouring such a huge subarachnoidal cyst, and because of the paucity of the clinical experiences recorded, the report of the clinical and operative features of this case is presented as material which may shed some light on the controversial problem of the origin and pathogenesis of this condition.

Clinical History

Case GA (No. 128882).—A boy aged 10 was admitted on August 21, 1959, with a long history of intermittent bitemporal headaches which had recently increased in intensity.

The family history contributed nothing.

The boy's birth and subsequent development were relatively normal, and, except for three successive attacks of pneumonia at the age of 2, he had had no previous illnesses.

At the age of 3 he had fallen out of his bed and lost consciousness for a short time. No exact details on this point could be obtained, but apparently there were no after-effects until three months later, when he was first noticed to have a bony prominence anterior to and above the right ear. From then on the child became emotionally unstable and gradually developed enuresis, showed outbursts of aggressive and hyperkinetic behaviour, and was generally rather difficult to manage. He had no convulsions, attacks of unconsciousness, or automatisms.

At the age of 5, left convergent strabismus became evident and from then on the child started to wear glasses; nevertheless, the visual acuity in the left eye progressively deteriorated.

He reached school at the age of 7, but failed to make proper progress, and at that time began to complain of

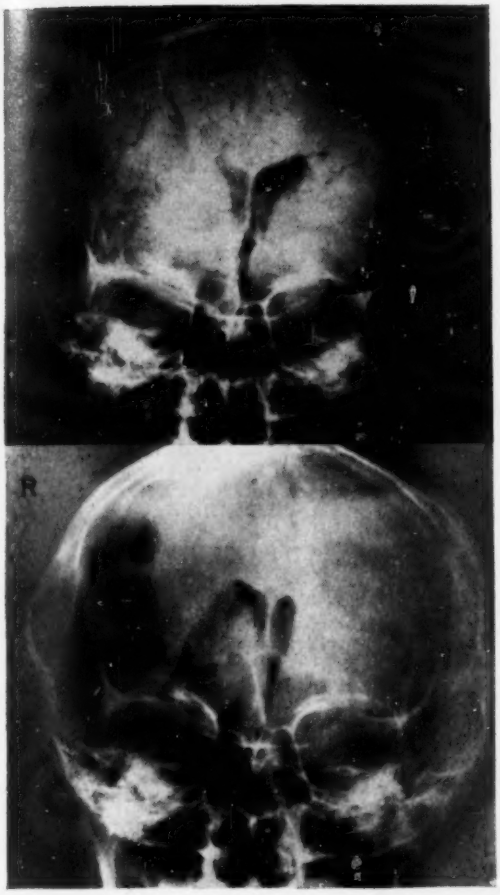


FIG. 1.—(a) Antero-posterior pneumoencephalogram showing slight shift of the septum pellucidum to the left and asymmetry of lateral ventricles, the right being smaller than the left.
(b) Right temporal pneumoencephalogram (short view) showing elevation of the temporal horn tip and increased distance between it and the inner aspect of the enlarged skull, but normal relation of the former to the midline structures.

headache localized in both temporal regions. As they had lately become more frequent and had gradually increased in intensity, further attention was paid to the bulging of the right temple and it was thought at that time that it had become more marked.

Physical examination revealed a pale-looking boy of lower level-normal intelligence. The right anterior temporal region was markedly prominent. The chest was clear to percussion and auscultation. The heart was not enlarged, its beats were regular and no murmurs were audible. Blood pressure was 115/70 mm.Hg. The abdomen was soft, the liver and spleen were not palpable, and the genitalia were normal.

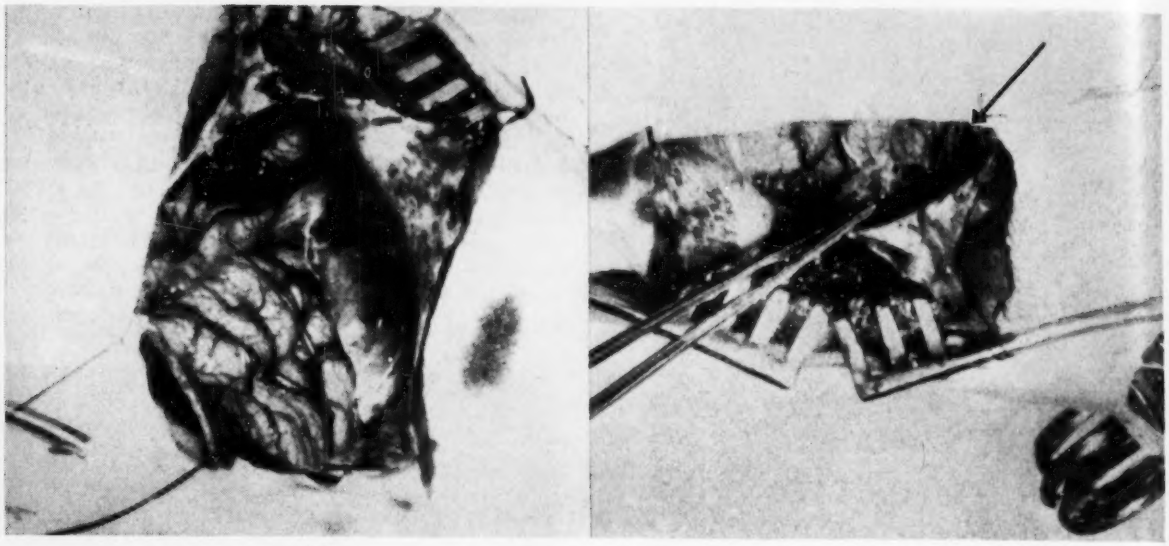
The neurological examination was negative except for hyperactive deep reflexes on the left side.

Eye examination revealed signs of hypermetropic astigmatism. Visual acuity with the patient wearing glasses was 20/20 in the right eye (+6·0) and 20/200 in the left (+6·5 = 2·0 cyl. 80°).

Laboratory findings of blood and urine were within normal limits and a radiograph of the chest was normal.

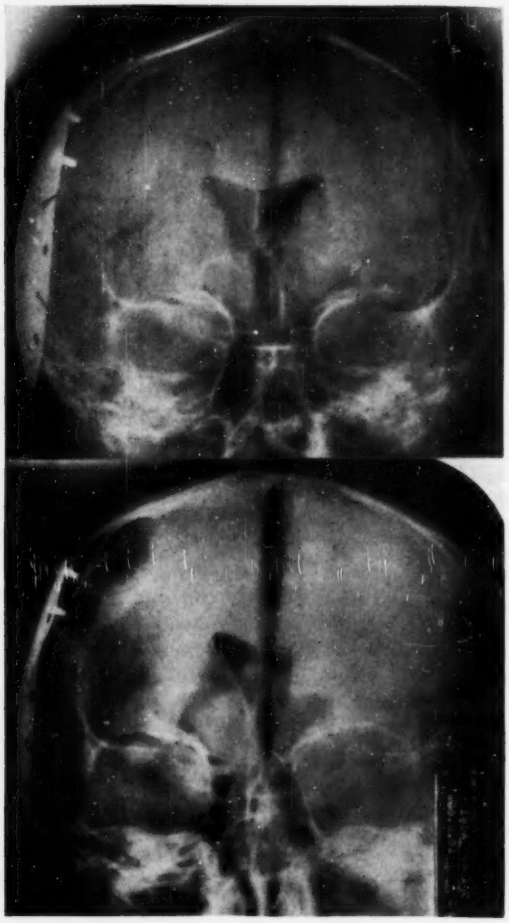
Radiographs of the skull showed pronounced outward bulging of the right temporal region with thinning of the bone, elevation of the right lesser wing of the sphenoid, and marked forward enlargement of the right middle cranial fossa. There were no radiological signs of generalized increased intracranial pressure. An E.E.G. showed decreased amplitude, slow wave focus over the right temporal region. Pneumoencephalography revealed that the septum pellucidum was slightly shifted to the left, the right lateral ventricle being smaller than the left. Moderate elevation of the right temporal horn tip was apparent, the length of the temporal horns being obviously unequal. Moreover, the subarachnoid pattern over the right temporal lobe was lacking and the distance between the inner table of the bulged right temporal squama and the right temporal horn was markedly greater than on the left side (Fig. 1). The cerebrospinal fluid removed during this procedure was clear and contained 27 mg. of protein per 100 ml. Right carotid angiography demonstrated that the anterior cerebral artery was slightly displaced to the left and that the middle cerebral artery and its branches were markedly displaced medially and upward. Between the inner table

FIG. 2.—Antero-posterior right carotid angiogram showing slight shift of the anterior cerebral artery to the left and marked displacement of the middle cerebral artery upward and medialward. Note the obvious asymmetry of the skull.



(a) (b)

FIG. 3.—(a) Operative field after aspiration of the cystic fluid to show the antero-lateral aspect of the temporal lobe in relation to the enlarged middle fossa. (b) The tip of the bayonet forceps is pointing to the delicate trabecular connective tissue network through which potential communication existed between the cyst's cavity and the general subarachnoid space.



(a)

(b)

FIG. 4.—(a) Post-operative pneumoencephalogram showing slight symmetrical dilatation of the lateral ventricles and their shift to the side of the lesion.
(b) Right temporal shot view to show normal length of the temporal horn.

of the skull and the brain there was an avascular area (Fig. 2). In the lateral view, the elevation of the middle cerebral vessels was not as pronounced as the antero-posterior film suggested.

The clinical findings raised the possibility of a long-standing, slowly progressive intracranial expanding lesion and a pre-operative diagnosis of chronic post-traumatic arachnoidal cyst was taken into consideration.

Operation.—Through a linear incision, a trephine opening was made over the middle of the bulged temporal bone, which was found to be of eggshell thickness.

After enlarging the burr opening, a circular skull defect 6 cm. in diameter was obtained exposing a bluish, tense dura mater. It was punctured and about 40 ml. of clear colourless fluid was withdrawn. The dura was then incised and opened in the usual manner, resulting in the exposure of a huge thin-walled cystic cavity that occupied the entire anterior portion of the middle cranial fossa as well as the outer third of its middle part. It contained as much as 150 ml. of clear cerebrospinal-like fluid of which the protein content was 53 mg. per 100 ml.

After complete evacuation of the fluid, the size of the right temporal lobe appeared to be rather small in relation to the markedly enlarged middle fossa, but its configuration, including the gyral pattern, was of normal aspect. There was no lining covering the temporal lobe and it was evident that the membrane representing the lateral wall of the cyst was continuous with the arachnoid overlying the cerebral cortex.

A delicate trabecular connective tissue network connected this membrane to the pia of the temporal lobe 4½ cm. posteriorly from its tip, and along the posterior part of the Sylvian fissure, allowing some communication between the cyst's cavity and the subarachnoid space overlying the neighbouring cerebral convexity (Fig. 3). The empty anterior portion of the middle fossa measured 4·5 cm. in length and 3·5 cm. in width. The distance between the dura and the convexity of the temporal lobe gradually decreased from its tip backward. The lateral wall of the cyst was partially adherent to the inner lining of the dura from which it could be easily separated, and part of it removed for examination. In order to relieve the tension exerted on the underlying cortex, free communication between the relatively closed cavity of the cyst and the general subarachnoid space was obtained by careful separation of the adhesions between the pia mater and the lateral wall of the cyst. No expansion of the temporal lobe could be observed. After water-tight closure of the dura, the bone defect was covered by a plate of stainless steel and the wound closed in the usual fashion.

The histological examination showed a membrane similar to arachnoidea, with scattered psamona bodies.

The child's post-operative course was uneventful, the headaches did not recur, the enuresis completely disappeared for a period of three months, when it recurred, appearing at longer intervals.

Pneumoencephalography performed nine months after operation showed symmetrical dilatation of the lateral ventricles and equal length of both temporal horns (Fig. 4).

The clinical improvement was accompanied by the disappearance of the abnormal pattern in the E.E.G.

Discussion

Large, pseudo-tumoral, chronic arachnoidal cysts of the middle cranial fossa accompanied by local enlargement of the skull represent a clinico-pathological entity which, surprisingly, has seldom been reported in the medical literature.

Besides the cases presented by Childe at the 52nd annual meeting of the American Roentgen-Ray Society and published in 1953, only a few cases of this particular type of lesion had been previously reported.

In 1955, two additional cases of localized collections of fluid, accompanied by thinning and bulging of the temporal squama as well as enlargement of the middle cranial fossa, were reported by Robinson, who emphasized the apparent developmental origin of these cysts and their unequivocal location in the subarachnoid space. The ratity of this condition is stressed by the fact that in his review of the world literature, he was unable to find more than 15 similar cases up to that time. His series does not include the case of Briusova (1951) reported in the Russian medical literature.

More recently, the developmental origin of some of the large arachnoidal cysts has been supported by the pathological findings, incidentally encountered in three cases at necropsy by Starkman, Brown, and Linell (1958).

In the same year, another five cases were reported by Robinson (1958), in three of which large collections of fluid resembling cerebrospinal fluid localized in the middle cranial fossa were associated with bulging of the overlying temporal bone. He suggested for this condition the term 'external hydrocephalus', which, in his opinion, was secondary to the agenesis of the temporal lobe.

That such a conclusion may not be warranted in all cases is suggested by the fact that signs of previous subdural bleeding were found in Childe's (1953) Cases 2 and 3 as well as in those of Cohen (1927), Hardman (1939), and Pertuiset and Berdet (1952), included by Robinson (1955) in his first series of cases. Moreover no local enlargement of the skull was present in Case 4 of Robinson (1958) as well as in the cases of Starkman *et al.* (1958), while in Robinson's (1958) Case 7 no neuroradiological investigations were performed at all, nor was the condition confirmed by surgery. The above-mentioned cases did not fulfil thereby either the radiological or pathological criteria characteristic of the type of arachnoidal cyst under consideration.

Analysis of the remaining 17 recorded cases showed that bulging of the temporal squama was the main complaint in all but one instance. In five of the cases this was the only change revealed in radiographs of the skull, while in the others, including our own case and the one in which no bulging of the temporal bone was mentioned, enlargement of the middle cranial fossa was present as well.

In only seven of the above cases did symptoms and signs of variable neurological deficit dominate the clinical picture. In reviewing all the recorded supratentorial arachnoidal cysts, we came to the conclusion that two factors at least are responsible for their occurrence, namely, a primary cerebral developmental defect, in which limited regions of the brain are missing and simply replaced by cerebrospinal fluid, the resulting fluid-filled cavities being in free communication with the general subarachnoid space. In these cases, the pressure of the collected fluid is not increased and consequently no secondary cranial changes occur. Moreover, associated porencephaly, hydrocephalus, or other malformations of the brain are usually present. Secondly, a mild closed head injury during early childhood, in which cases the clinical picture is characterized later in life by symptoms of cerebral compression and signs of localized bone changes, as in our patient.

Although there is no objective evidence to support the proposition that trauma of the head in early life is the responsible factor for this condition, such a possibility cannot be denied. It is generally thought that during a head injury the supratentorial structures of the brain are able to move through the tentorial openings. The temporal lobes, however, are withheld by the bony floor of the middle cranial fossa as well as by the tentorium itself. It is presumed that during the shifting of the brain in the direction of the impact, the contusion of the temporal lobe tip or of the hippocampal gyrus is accompanied by a small subarachnoid haemorrhage that later on becomes partially encapsulated in the anterior part of the middle fossa. As the protein molecules disintegrate, there is an increase in the osmotic pressure, and blood serum as well as cerebrospinal fluid is drawn in. In the course of time, as communication between this collection and the general subarachnoid space is partially maintained, absorption of the blood is possible and further accumulation of cerebrospinal fluid permitted.

It appears probable that the thinning and bulging of the temporal bone as well as the forward enlargement of the middle fossa occurs as a result of the continuous intracranial arterial pulsating pressure, transmitted to the endocranium by the local accumulation of fluid. This view is consistent with the opinion of List and Pendergrass expressed in the discussion following the paper of Childe (1953). It is assumed that these changes occur during early childhood, when the middle fossa may adapt itself to the enlarging cyst, similar to the moulding of the inner table of the skull by the growing brain.

When a history of trauma cannot be ascertained, the clinical diagnosis of chronic arachnoidal cyst is virtually impossible. Since superficially situated gliomas (Jupe, 1938; Orley, 1949), or subdural haematomas (Davidoff and Dyke, 1938), or chronic subdural hygromas (Hardman, 1939) may at times produce in children the same bony changes as are found in cases of arachnoidal cysts, one can only assume that a tumour or other intracranial slowly expanding lesion is present. In such cases even pneumoencephalography or angiography may be useless and only the placing of an exploratory burr hole over the bulging of the skull will reveal the real nature of the lesion.

There are as yet differences in opinion concerning the necessity to open and drain these cysts. There is no doubt that when the condition is asymptomatic, as it usually is in cases in which the cyst results from a developmental defect of the brain or meninges, there are no indications at all for surgery. However, in cases like our own, in which the cyst plays the role of an expanding lesion, complete aspiration of the fluid and careful separation of the arachno-cortical adhesions is, in our opinion, mandatory in order to improve the actual clinical syndrome and prevent further cerebral damage from reaccumulation of fluid.

The mild post-operative symmetrical dilatation of the lateral ventricles and their slight shift to the side of the previous lesion, as revealed in our patient by pneumoencephalography, is in keeping with the concept of an 'ex-vacuo' expansion of the brain.

Moreover, the equality in length of both temporal horns is an undoubted indication that, in this patient, there was no deficiency whatsoever of the temporal lobe. In our opinion this objective finding is a strong argument against the generally accepted view of a developmental origin for the chronic arachnoidal cysts of the middle fossa associated with the aforementioned bone changes.

Summary and Conclusions

A case of chronic pseudo-tumoural large subarachnoid cyst of the middle cranial fossa in a 10-year-old boy has been presented in order to illustrate this most unusual benign intracranial space-occupying lesion, in which trauma of the head seemed to be the aetiological factor.

While the actual mechanism is still debatable, subarachnoid bleeding (in the middle fossa), brain oedema, and any interference with the normal blood-brain barrier's function that might have resulted from the concussive force are to be considered significant contributory factors in the pathogenesis of this cyst.

In a review of the literature, only 17 similar cases have been found. With our own case the total number of the reported cases rises to 18. Whether these figures represent the true incidence of the condition or not, is doubtful, since chronic arachnoidal cysts are as a rule silent.

The probability that trauma of the head in early life is the responsible aetiological factor of this condition cannot be excluded, in spite of the fact that no history of head injury could be obtained in about 50% of the above cases. It is assumed that in those cases in which no history of trauma has been mentioned, minor traumas in the past could have been overlooked.

Symptoms varying from headache and irritability to a full temporal lobe syndrome, as present in this case, and local bone changes characterized by thinning and bulging of the temporal squama, as well as widening, deepening, and lengthening of the middle cranial fossa, may develop.

As a rule, the presence of the lesion cannot be established by clinical observation only. Although not pathognomonic for this condition radiographs of the skull, air studies of the ventricular system as well as cerebral angiography, are sufficiently characteristic to help in diagnosis. Ultimately, however, the condition can be diagnosed with certainty only by direct inspection.

The treatment of this lesion, in spite of its benign evolution, is surgical and the prognosis is usually good.

An alertness to the possibility of this intracranial, space-occupying lesion may result in an increased number of such cases being disclosed.

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PROCEEDINGS OF THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS: 62nd MEETING

The 62nd meeting of the Society was held on November 25-26, 1960, at the Morriston Hospital, Swansea. The President, Mr. D. W. C. Northfield, was in the Chair.

Arteriovenous Fistulous Aneurysms

NORMAN WHALLEY (Swansea) reviewed 50 examples of carotico-cavernous fistulous aneurysm. Ten of the cases had been treated in Morriston Hospital in the past nine years. The remaining cases were studied by permission of the late Sir Geoffrey Jefferson (26) cases, Mr. G. F. Rowbotham (12) cases, and Mr. J. Dutton (2) cases. After brief mention of the symptoms and physical signs in this condition he dealt at some length with the diplopia and ocular paresis which is such a common finding.

He went on to give in some detail the results of operative treatment. The figures quoted showed that the best results were undoubtedly obtained by the combined operation of internal carotid artery ligation in the cervical region and intracranial clipping of the internal carotid artery.

Seven of the 50 cases became arrested spontaneously and the problem of spontaneous closure of carotico-cavernous fistulae was briefly discussed.

The Treatment of Cervical Spondylosis

LAMBERT ROGERS (Cardiff) said that in 1892 Sir Victor Horsley had performed decompressive laminectomy for a patient in whom he found a 'hard bar' at the level of the sixth cervical vertebra. Recovery gradually took place over the course of the following year. This was probably the first recorded case of operative treatment for cervical spondylosis and he was indebted to Sir Francis Walshe for drawing his attention to it.

Myelopathy in cervical spondylosis was produced by the hard bars or ridges, the result of degenerative intervertebral discs projecting into the anterior part of the spinal canal, usually between the fifth and sixth and the sixth and seventh cervical vertebrae. With movements of the neck, repeated minor injuries to the cord or the anterior spinal artery took place and the cord tended to become like the brain of the professional boxer ('punch drunk'). A narrower spinal canal than normal might be contributory. Despite Horsley's successful operation local decompressions in the region of the ridges were generally disappointing and because of the danger to the cord it was impracticable to attack the hard bars. An alternative procedure had accordingly been devised. The results of its application were encouraging and no untoward results had been observed. Laminectomy from the atlas to the first thoracic vertebra was performed, the dura was opened throughout, all the dentate ligaments on either side of the cord were divided, it having been shown that the cord could thereby be freely mobilized. The dura was left open, the post-vertebral muscles approximated a little posterior to the open dura so as to enlarge the spinal canal and the patient nursed head downwards for three days to keep the enlarged canal full of cerebrospinal fluid and the cord thereby isolated. There was no subsequent weakness of the cervical spine. The procedure was one of mobilizing the complete cervical cord into an enlarged spinal canal.

Pott on Head Injuries: A Neurosurgical Bicentenary

J. POTTER (Manchester) described to the Society some of the work on head injuries published by Percival Pott 200 years ago.

Hydrocephalus Due to Cerebral Tumour in Infancy

D. J. B. ASHLEY (Swansea) discussed dilatation of the ventricular system consequent upon intracranial neoplasm. He stated that this was not uncommon in the adult but in children was an unusual phenomenon.

A case was described of a girl aged 10 months who had developed normally until the age of 7 months when she began to show signs of raised intracranial tension. The presence of hydrocephalus was confirmed by ventriculography which showed displacement of the ventricular system to the left and a reduction in size of the third ventricle. At operation a cystic subdural cavity was found in the right temporo-parietal region; section of part of the wall of this cyst showed it to comprise fibrous tissue. One week after the operation the condition of the child deteriorated and she assumed the position of decerebrate rigidity which she maintained until she died.

At necropsy a botryoid tumour was found occupying the whole of the base of the brain anterior to the pons. Sections showed this to be a pilocytic astrocytoma. No lesion was found in the cerebellum.

Pilocytic astrocytoma was one of the less common types of glioma. Russell and Rubinstein described an adult type and a juvenile type of piloid astrocytoma. The former, usually including within it other types of glial cells, occurred mainly in the brain-stem, hypothalamus, and cerebellum and was sometimes seen in association with neurofibromatosis. The juvenile type, to which this lesion was assigned, comprised spindle-shaped cells showing a tendency to form longitudinal investments of the blood vessels with hypocellular areas away from the vessels.

The nature of the temporo-parietal cyst in this case was obscure. It could have been a cystic portion of the tumour but the more likely explanation was that it was a second intracranial lesion, a subdural cyst, and that the hydrocephalus was due to a combination of the effects of the two lesions.

Reinforcement of Intracranial Aneurysms with Adherent Plastics

B. SELVERSTONE (Boston, Mass.) said that aneurysms which had no neck and were so situated that they could not be trapped without producing cerebral infarction had usually been treated by wrapping with muscle or gauze in the hope that protective perivascular fibrosis would occur. Little support had probably been afforded during the period when recurrent haemorrhage was most likely. A method was therefore sought which would provide immediate reinforcement of the wall of an aneurysm by means of a flexible, adherent coat which would not compromise the patency of vessels entering and leaving the sac. It was found that an artificial 'latex' consisting of a microdispersion of polyvinyl-polyvinylidene chloride co-polymer in distilled water could be sprayed by means of an artist's airbrush to leave, when dry, a thin, flexible transparent coat on a blood vessel or aneurysm. This film was intimately adherent so that it could not be removed without taking adventitia with it; it was dimensionally stable and well tolerated by the tissues. It provided relatively little strength but left a dry surface with which an epoxy-polyamide resin could form a firm bond. The resin used for the second or reinforcing coat was also well tolerated by the tissues and was dimensionally stable, flexible, and resilient. No significant rise in temperature occurred during the polymerization of either coat.

Fourteen craniotomies for aneurysm were reported, in 10 of which the method was used to coat an aneurysm without sacrifice of feeding vessels. Of these, six were at the middle cerebral 'trifurcation', one of the anterior communicating artery, with both anterior cerebrals entering and leaving the sac, one of the posterior communicating artery, and two of the internal carotid. In each case, the aneurysm was exposed under hypothermia, with temporary occlusion of appropriate vessels when necessary. Bleeding points, if any, were controlled with small silver clips on the edge of the sac. The sac and adjacent parts of vessels entering and leaving were then coated, first with the spray of vinyl polymer and then with the epoxy-polyamide resin. The wound was then closed, allowing the second coat to complete its polymerization after closure. Of the 10 patients so treated, seven were classified as excellent results (fully employed) and three as good results (working part-time and without major neurological disability). Of the four cases in which it was necessary to sacrifice major vessels in order to control bleeding from the aneurysm, one was dead, one was a poor result, one was classified as good, and one excellent.

The Use of Quick-setting Dental Acrylic in the Skull

I. N. MACIVER (Newcastle-upon-Tyne) described the use of quick-setting dental acrylic and said that working in a unit which dealt with a large number of head injuries had shown that the so-called 'defect syndrome' was a very real problem and led to much unhappiness, loss of work, and domestic difficulty. In order to combat this syndrome it was essential to fill in the defect as soon as possible.

Although the use of autogenous or heterogenous bone or tantalum gave satisfactory results, the use of quick-setting dental acrylic enabled certain defects to be dealt with at the time of operation and the remainder could be dealt with in a one-stage operation before the patient left hospital.

The present technique used was based on that described by Woringer in 1951 with the exception that the acrylic when setting was immersed in warm saline to prevent excessive evaporation and to allow it to be removed freely from the vehicle in which it was mixed, and in addition no protection to the soft tissues of the scalp had been found to be necessary. The shape of the graft could be moulded by layers of gel foam placed below it. The main question had been that of sterilization; Woringer considered that the chemical properties of the monomer and the process of polymerization would kill off all organisms apart from *Cl. Welchii*. In 1953, at his request 0·5% mercurochrome was added by Dental Fillings Ltd. to the original acrylic powder to make it self-sterilizing and this powder was mixed directly with the monomer liquid without sterilization.

In 1954, Robinson and Macalister, of the Dunedin Hospital, and the University of Otago Dental School, N.Z., suggested that only the growth of *Cl. Welchii* was inhibited after two hours by the acrylic and that sterilization of the liquid should be carried out. Dutton had sterilized the powder by beta radiation from a cobalt bomb and had sterilized the liquid by passing it through bacterial filters.

In the technique described, the Woringer method using powder and liquid direct from Dental Filling containers and bottles had been used.

A total of 814 implants had been made if one counted a leucotomy as two separate grafts and each cosmetic flap as being an average of four small grafts. Only four cases had broken down and in none of these could evidence of primary infection of the graft be found. This method enabled an adequate graft of considerable size to be made easily and directly on the spot; it was achieved without fixation of any other type and appeared to be satisfactorily tolerated by the tissues. The defect syndrome could be completely avoided by its early use, and the patient rapidly returned to work without fear of injury to his brain.

Dyslexia

F. G. HIBBERT (Swansea) discussed a series of 27 cases with dyslexia, which he defined as a relative inability to appreciate the meaning of written words, musical notes, or mathematical figures. All had a developmental dyslexia in the absence of established organic disease.

Twenty-three of the cases showed left-handedness, usually ambidexterity with a preferential use of the left hand. There was a tendency in these cases to attribute primary causation to a developmental defect of speech

but he stressed that auditory speech was primary and visual speech dominated by it, visual words merely being symbols of auditory words which were, in themselves, symbols. In no case could a defect of auditory speech be found but there was a high incidence of defective articulation, generally limited to the pronunciation of 'th' as 'f' or 'v'. This defect of articulation was common in early childhood. Its persistence was part of the syndrome and often the first sign suggesting the nature of the case. It occurred in 16 of his cases. Disability in reading was the chief feature and this could accompany many defects of cerebral function. Excluding organic diseases this defect could be associated with limited intelligence, lack of schooling, inadequate motivation, sensory and neurological handicaps. All such factors were absent in this series. In the age group of this series, 8-13, there was a uniform reading age of 5 years but with normal intelligence quotients of 80+.

Arithmetic manipulation had caused some difficulty in the diagnosis of this condition, for the ability to recognize numbers, but not letters or words, was not served by the same faculty. In this series arithmetic manipulations were better than reading, though still showing a low age factor; the differing ability in the two functions was characteristic of the condition.

Psychological complications were common and arose from the fact that illiteracy in a bright child tended to cause abnormal relations between the child and surrounding persons. The manifestations were pleomorphic and bizarre and there was no uniform picture. No attempt at direct therapy was made by the psychiatrist but a brief explanation to child and parents often led to spontaneous improvement.

Mirror perception, in which the child was able to read single letters or sequences in reversed order without awareness of the error, was common. The patients were predominantly males and it was possible that specific dyslexia was genetically determined.

In many cases words were recognized by the familiarity of their picture but in every sentence, however simple, single words would baffle the child and the sense and subtlety were lost to him. The disability, therefore, usually presented not as a specific reading disability but as a problem of scholastic failure and behaviour disorder. A good memory, average insight, and a capacity to learn by aural instruction were features of the cases. It was possible that instruction along aural lines together with viva voce assessment of knowledge might open up a better future for many of these cases.

The syndrome could be summarized as a male child of 8 or more years who was left-handed or ambidexterous and had a normal I.Q. of 80 or more; whose reading age was very low, whose arithmetic age was low but higher than reading, who had a defect of articulation and mirror perception to a variable extent. There was reading and writing disability.

Experiences with Diastomatomyelia

P. M. H. Rack (Cardiff) reported a series of six children with diastomatomyelia who had been operated on in the Cardiff Royal Infirmary during the past four years, one boy and five girls. In all cases the spinal cord was found to be split in the lower dorsal or lumbar regions, but in only three of these did it re-unite within the exposed area. Transfixing spurs of bone were present in five cases and in one of these seemed to be tethering the cord. In another case the cord was tethered by adhesions and in a third was compressed between the spur and a pedicle.

The two cases in which the cord was tethered had deteriorated neurologically before operation and improved satisfactorily after operation.

Temporal Lobe Epilepsy due to Small Focal Lesions Associated with Bilateral Independent Spike-discharging Foci: A Study of Cases Relieved by Operation.

Murray A. Falconer (London) reviewed the clinical and E.E.G. features of seven patients with temporal lobe epilepsy, which was disabling and resistant to drug therapy and which was also associated with bilateral epileptic discharges on electroencephalography. The air encephalograms in these cases showed no direct evidence of tumour, but each presented some E.E.G. or radiological feature which indicated a lesion of one temporal lobe. All seven cases were therefore submitted to a unilateral temporal lobectomy. Subsequently, a minute unsuspected tumour was found in each case, while all cases had been strikingly benefited since, three being rendered completely fit-free, and four almost fit-free. The E.E.G.s returned to normal. The possible mechanisms by which these unilateral causes led to bilateral epileptic discharges were discussed, as well as signs by which similar cases could be predicted.

The Significance of Negative Investigations and Ventricular Dilatation in Cases of Brain Tumour

A. K. Omaya (Swansea) said that previous reports had stressed the occurrence of 'normal' radiological appearances in clinically suspect cases of brain tumour subsequently revealed as having frank space-occupying lesions. But the results of repeated investigations in such cases had not been reported adequately nor had the presence of generalized ventricular dilatation been noted. He then reported four cases of brain tumour, two gliomas and two metastatic carcinomas, which had behaved initially as space-replacing rather than space-occupying lesions and exhibited a degree of ventricular dilatation which led to a false assessment.

This ventricular dilatation was more evident on the side of the lesion, was not related to obstructive hydrocephalus nor was it compatible with the normal ventricular enlargement noted with increasing age. Ventricular enlargement had been noted as a radiological feature of lumbar air encephalography and had contradicted the clinical diagnosis of brain tumour in each case. Repeated investigations were demanded by the progress of the clinical picture after a short interval (one to six months) and indicated the presence of a tumour which was verified histologically in each case and by necropsy in two.

Excluding any obstruction to flow of cerebrospinal fluid on the basis of air studies and necropsy several

possible explanations were discussed. Excessive production of cerebrospinal fluid had been described in choroid plexus papillomas but had not been considered in other tumours. Defective absorption had to be considered in metastatic carcinoma and in tumours which had bled into the cerebrospinal fluid pathway as both these conditions might produce a low-grade meningitis or ependymitis. Atrophy secondary to degenerative and vascular changes in and around the tumour known to occur in gliomas did not explain the bilateral dilatation.

Finally, he put forward the hypothesis that this might be part of a generalized atrophic process in the white matter occurring as a pre-neoplastic stage in the development of a tumour which subsequently appeared at the site of maximal atrophy. He had no proof of this hypothesis but suggested that further histological studies in this field might be useful.

An Aetiology of Internal Carotid Artery Thrombosis

H. A. MASLOWSKI (Manchester) said the work on blood flow in the vertebral artery in relation to head and neck movement had suggested that such movements might also influence circulation in the carotid vessels, and he had been led to believe that mechanical factors played a major part in selecting the site of atheroma in the carotid arteries and elsewhere, and played a decisive role in precipitating thrombosis or ischaemic infarction distal to the stenosed segment of the artery.

He stressed that he did not equate mechanical factors with causes of atherosclerosis and the mode of formation of atheromatous plaques. He discussed these factors in some detail. He concluded that these plaques were related to injury or abnormality of the endothelium, enhanced tendency to thrombosis, and failure of fibrinolysis after the plaque had formed. These plaques needed their own blood supply, which was vulnerable, so that they were liable to necrosis and haemorrhage in their centres which could be the starting point of massive occluding thrombosis.

Excluding direct injury, the only trauma the arteries were subject to was stretch due to pulse waves and eddying of blood currents at bifurcations. Though these factors affected all vessels equally there were sites of election for atheroma and in the carotid arteries only a very limited area was commonly affected. He believed that mechanical factors—torsion, longitudinal stretch, and kinking produced by head and neck movements—were the main cause of atheroma at the lower end of the internal carotid. Intimal injury could occur at the sites of maximal localized stress, most likely torsional, and thus start a train of events leading to arterial stenosis and occlusion. Some previous reports bearing on this hypothesis were discussed.

The results of experiments on the dissected carotid tree, filled with Urografin and radiographed in various positions, and further experiments on cadavers tended to support this view. The common carotid was little affected by head and neck movement and the external carotid was tethered at its origin to some extent by the superior thyroid artery. With movement of the head, sometimes through 180°, the internal carotid must rotate and though this torsion was distributed throughout its length, owing to the tethering at the bifurcation, the maximal stress fell on its lower end. This torsional effect on the lower end of the internal carotid could be demonstrated by angiography during head movement in both the normal and stenosed carotid artery, and slides were shown to demonstrate it.

The Treatment and Prognosis of Optic Nerve Gliomas

R. TYM (Manchester) briefly described 10 cases of piloid glioma of the anterior optic pathways, followed for an average of 10 years in order to illustrate the frequent benign course of these neoplasms, both with respect to mortality and to morbidity. On the nine cases submitted to biopsy, all showed typical tumour structure and were histologically indistinguishable both from each other and from many other cases with piloid gliomas in other sites such as the cerebellar hemispheres.

The difficulty in giving a prognosis was stressed. Two patients died, but two others who had been treated neither by surgery nor radiotherapy, showed spontaneous improvement in vision over periods of 15 and 18 years. He said that no cases had been recorded in the literature where the follow-up period had exceeded 20 years from the time of partial removal, though many of the patients so recorded were well at that time.

As the long-term natural history of the tumour had not been made clear, especially with regard to the spontaneous improvement that may occur, the claims for surgical or radiation therapy were considered suspect.

The role of palliative surgery was discussed. For a tumour confined to one nerve total surgical removal was advocated.

The effects of radiotherapy were considered unproven.

The necessity of prolonged follow up of histologically or surgically verified cases was emphasized, for the possibility existed that a glioma of the anterior optic pathways, presenting in childhood, might be compatible with a normal life span without necessarily being totally removed or irradiated.

Referred Pain in Spinal Whiplash Injuries

GEOFFREY KNIGHT (London) said that referred pain from spinal articulation and ligaments affected by whiplash injuries was mediated by the recurrent branch of the ramus meningeus and the posterior primary divisions; the latter supplied the intraneural, articulatory, and interspinous ligaments.

'Traumatic occipital neuritis' was an example of referred pain from the upper cervical joints mediated by the occipital nerves and frequently followed head injuries. The pain when passing through the vertex and forward to the eye was increased by placing the head in maintained postures, and on account of the flexed attitude adopted for reading or writing often appeared to be increased by mental concentration. Reference to the eye was accounted for by peripheral overlap between the cervical and trigeminal areas. Pain in a similar distribution accompanied high cervical arthritis. Relief could be obtained by occipital neurectomy, which in arthritic cases was performed distal to the site of the lesion, indicating that for referred pain to be experienced, the

area to which the pain was referred must receive innervation.

Pain referred to peripheral areas in the limbs arose from disturbance of deep articular structures innervated by the posterior primary division.

Interspinous ligament injury produced a more localized midline pain.

Marginal fractures of the cervical facets caused pain referred to the whole of the corresponding dermatome from involvement of the posterior primary division, which might be relieved by excision of the detached bone at facetectomy.

Referred pain in the shoulder and arms resulting from cervical whiplash injuries might be relieved by restricting movement in the affected joints by a paraspinal acrylic inlay.

Excision and injection of interspinal ligaments might relieve local pain in the dorsal region and certain forms of sprung back.

Severe referred pain in the lower limbs originated from unstable joints in the lumbar spine.

In cases of chronic low back pain and reflex sciatica, with normal neurological findings, radiographs and normal myelogram, exploration of the lumbar spine might reveal evidence of abnormal stretch and mobility between spines and vertebra. Insertion of paraspinal inlays might then afford relief.

The Use of Barium Sulphate in the Visualization of Cerebral Abscesses

P. R. R. CLARKE and S. WRAY (Middlesbrough) reported the use of sterile micropaque barium sulphate as a constant medium for injection into cerebral abscesses.

Three cases were described in which satisfactory visualization of the abscess cavity had been obtained. One patient had died six months after treatment and histological findings were presented. These showed that barium sulphate was taken up in phagocytes which stayed well localized and showed only minimal local migration. These barium-containing phagocytic aggregations stimulated a fibrous tissue reaction but not a glial reaction.

It was concluded that sterile micropaque barium sulphate suspension was a satisfactory alternative to Thorotrast as a substance for injection into brain abscesses.

The Third Optic Nerve

BRODIE HUGHES (Birmingham) showed pathological material from four cases in which there appeared to be a third optic nerve extending forwards a short distance from the anterior aspect of the chiasma. These were chance findings at routine post-mortem examinations.

He concluded from histological material that these projections were in fact merely loops of crossing fibres which did not, as is usual, loop into the optic nerves and tracts. He suggested that in these cases the crossing fibres had become separated from the uncrossed and that this was a progressive feature in human anatomy. If this were so one might expect an increasing dissociation between crossed and uncrossed fibres in the optic nerves and chiasma and more examples should appear in the future. A knowledge of this anomaly might be useful in interpreting field loss from parachiasmal lesions and in understanding the situation if such an anomaly were encountered at operation.

BOOK REVIEWS

Sir Geoffrey Jefferson: Selected Papers. (105*s*.) London: Pitman Medical Publishing Co. 1960.

Many members of the Society of British Neurological Surgeons will recall the occasion at Trinity College, Dublin, when Sir Geoffrey Jefferson delivered his lecture on René Descartes. It gave us pleasure then to applaud the scholarship and to have demonstrated to us so vividly how wide the canvas of medicine can be. This lecture, and other general and philosophical addresses printed in the first part of this volume will attract a wide readership and are destined to have a permanent place in our medical reading. They reflect the extent of Sir Geoffrey's contribution as an ambassador of neurological surgery. The next section of the book contains historical addresses, and the author's articles on MacEwan, Horsley, and Cushing put the history of the young specialty of neurological surgery into perspective, and prepare for the third section which is devoted to formal clinical papers. The rapid development and drive of neurosurgery during these last 30 years can well be judged from these articles. Sir Geoffrey's main interests have been the tentorial pressure cone (the 1937 paper is reprinted here), lesions of the sellar region, and the problems of subarachnoid haemorrhage and aneurysms. The papers on this last topic show the mature reflections on this difficult subject, together with the almost youthful enthusiasm for a fresh approach and the then new possibilities of surgical attack. Throughout the book and in this section, too, we are constantly reminded of how much in medicine we stand on the shoulders of those who have gone before.

In a characteristic little vignette at the end of this volume, Sir Geoffrey declares himself happy and to have had a happy life 'as a by-product . . . of something that one does and is incapable of pursuit in itself'. We are also fortunate that in this country the developing years of neurological surgery also produced a great scholar surgeon who could write it down, make his own considerable contribution, and stimulate the young men of the future. Yes, a happy life.

Modern Scientific Aspects of Neurology. Edited by John N. Cumings. (Pp. 360; illustrated. 65*s*.) London: Edward Arnold. 1960.

Some of this book will be above the heads of clinical neurologists. Nevertheless, most clinicians will find parts of it written in terms which are familiar and relevant to interests of their own. Its main value lies in illustrating how modern scientific methods and ideas have been, and will be increasingly, applied to clinical problems. Much of it is devoted to cytochemistry and cytoanatomy, the results of electron microscopy and newer differential staining techniques being described. Increasing complexity of structure and function is the keynote that emerges. The book illustrates the point that science is international. Of the 11 contributors, four come from English medical schools and the rest from various European countries. It will be of value to those engaged in clinical research on the nervous system, the very full references in each section being especially useful.

Neurochemistry of Nucleotides and Amino Acids: A Symposium of the Section on Neurochemistry, American Academy of Neurology. Edited by Roscoe O. Brady and Donald B. Tower. (Pp. xiii + 292; 62 figures and 64 tables. 80*s*.) London: Chapman & Hall. 1960.

This symposium was held at the 1958 annual meeting of the American Academy of Neurology, and is of course intended for the biochemist. The papers are excellently presented, and both papers and discussion are supported by an extensive bibliography and index. The techniques for investigating individual regions of the brain are quite remarkable, and even the microsomes themselves have been separately studied.

The wealth of specialized information is likely to leave the clinician bewildered, but he will find much of interest and encouragement in certain sections. Knowledge of the importance of specific nucleotides in lecithin metabolism and myelin formation brings hope for a new understanding of the demyelinating and degenerative disorders. There is little information about the derangements of metabolism in pathological material, but where this has been undertaken the results would seem to have immense importance to neurology and psychiatry. Interesting work is reported on the role of asparagine and glutamic acid in human epileptogenic cerebral cortex, and on the relation of pyridoxine-dependent convulsions to gamma amino butyric acid formation in circumscribed areas of the brain.

Already, awareness of altered galactose metabolism (possibly dependant on uridine nucleotides) and phenylalanine metabolism has made inroads into the formerly barren field of mental defect.

Such is the growing importance of these two branches of neurochemistry, and the present book is a valuable and stimulating contribution.

Somatosensory Changes After Penetrating Brain Wounds in Man. By Josephine Semmes, Sidney Weinstein, Lila Ghent, and Hans-Lukas Teuber. (Pp. xiii + 91; 9 figures. 32*s*.) Harvard University Press (London: Oxford University Press). 1960.

The correlation of clinical signs with anatomical lesions is traditional in neurology. Hitherto such

correlations have been made in individual cases, or in groups selected on the basis of the site of the lesion. Neurology has been tardy in utilizing modern methods of experimental design and analysis, which eschew preconceptions, and seek to control and validate every step in the process of observation and deduction. This lacuna has been filled in a most efficient manner by the work of Dr. Teuber and his associates, which is reported in this excellent monograph.

They have concerned themselves here with punctate pressure, two-point discrimination, and point localization, making use of exact quantitative methods of measurement. They have obtained objective norms by testing a group of patients without brain wounds, and have thus been able to assess the significance of the deviations shown by their group of patients with penetrating brain wounds. The relationship of an abnormality in the test result to a lesion in a specific site has been ascertained by comparing it with the results obtained from lesions in other sites. The possible influence of such factors as intellectual deterioration, epilepsy, and dysphasia has also been evaluated. Thus in design and execution this study is a model.

The most astonishing finding was that the two cerebral hemispheres are not homologous with regard to the tests of sensation applied in this study. In the normal control group the sensitivity to punctate pressure was less in the right (preferred) hand than in the left. In the brain-wounded group, while defects in sensation in the right hand could be correlated with lesions of the opposite sensorimotor cortex, this was not so of the left hand. The evidence suggests that sensation is subserved diffusely in the right hemisphere. Moreover sensory defects in the left hand were often produced by lesions of the ipsilateral sensorimotor cortex.

Thus former analyses of the nature of sensory abilities and defects on an intensity-extensity basis, and previous attempts to relate these categories to complex tasks of discrimination, all of which were based on the assumption that the hemispheres were homologous, must be revised. But more important for neurology than the results obtained, is the lesson that historic methods must give place to modern techniques, and with them will go many of our cherished illusions about the brain and its function.

Inheritance of Glioma. By H. J. Van Der Wiel. (Pp. 275. 63*s*.) Amsterdam: Elsevier; London: D. Van Nostrand. 1960.

In order to determine whether a genetical factor might play some part in causing gliomas, the author ascertained whether the frequency of certain familial abnormalities is greater in the relatives of glioma patients than in a control group. The constitutional anomaly chosen for this purpose is called status dysraphicus, which comprises deformities of the sternum, kyphoscoliosis, myelodysplasia, an accessive proportion of span to height, and various deformities of palate, digits, limbs, hair growth, etc.

One hundred patients with verified gliomas formed the basis of the investigation; full details of the relatives—grandparents to grandchildren, brothers and sisters, aunts and uncles, nieces and nephews and cousins—were obtained and all those alive in the Netherlands were visited. There were 5,262 relatives, of whom 1,290 were dead; 3,557 were examined for stigmata of status dysraphicus and the findings classified. The control group consisted of the relatives (2,228) of 100 randomly chosen families, and these were similarly examined. Of the 1,290 dead relatives of the glioma patients, seven had died of glioma and in five others death was probably due to a glioma. Amongst the dead relatives of the control group there was not a single case of glioma. In the control group of relatives 7·8% show features of dysraphism; in the near relatives of the glioma group this proportion was 20·8%, among cousins it was 13·4%. The frequency of café-au-lait spots in the glioma group of relatives was much higher than in the controls. The findings, and the observations of other workers 'have led the author to the conception that gliomas are manifestations of an endogenous blastomatosis'.

This book records the results of much labour, involving personal travel, many thorough physical examinations, statistical evaluation, and the cooperation of thousands of individuals who might reasonably have wondered why. The book is well produced and is written in an easy and interesting style in spite of the somewhat indigestible material; it includes an excellent review of other publications on this subject. Dr. Van Der Wiel is to be congratulated.

Primary Tumours of the Calvaria. By Franklin Jelsma. (Pp. x + 116; illustrated. 56*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1959.

This small book presents the author's own experience of 49 cases of various types of tumour. It is well written freely illustrated, and the clinical accounts of quoted cases are well documented, including the long-term results of treatment. A useful bibliography is given. Considering its modest size, it is very expensive.

Essential Tremor. By T. Larsson and T. Sjögren. (Pp. 176; illustrated.) Copenhagen: Ejnar Munksgaard. 1960.

This is a fascinating study of the occurrence of essential tremor in a population of northern Sweden. The high incidence of the disorder in this part of the country and the rather stable population made the investigation very worthwhile from the genetic standpoint. Most of the families had dwelt in the area for centuries, the people were aware of the hereditary nature of the disease, and concurring data were obtained about the existence of the disease in ancestors, in two instances in individuals who had died over a hundred years before. The clinical description is thoroughly validated by the examination of 87 cases.

Bird-Headed Dwarfs. By Hilmut P. G. Seckel. (Pp. viii + 241; 64 figures. S. fr. 54.-.) Basel and New York: S. Karger. 1960.

This is a study of two dwarfs of a rare type whose chief feature is that their proportions of skull, face, and body are those of normal adults despite their extremely small stature. They are born dwarfish and although

Virchow characterized them as "nanocephalic" or "bird-headed" it is worth noting that of the 15 well-recorded cases in the literature only 12 had the large protruding nose and only 10 the receding chin which together give a "bird-like" profile. Mental retardation was present but not found to drop within the range of microcephalic idiots, and congenital malformations were common. A familial tendency was noted: endocrinological tests were unrevealing, and endocrine therapy ineffective. The first purpose of the monograph is complete objective and numerical documentation, and the monograph accordingly comprises a mine of somatometric, cephalometric, psychometric, and other indices, yet data for the first dwarf extends only to the age of 9 years and for the second only from 14 to 35 months. As to pathogenesis, cellular haploidism is excluded by proof of normal blood and epidermal cell size, and the theory is advanced that a hypothetical gene operates by decelerated cell division both in the embryo and subsequently.

The Essentials of Perimetry. By Howard Reed; Foreword by Arnold Sorsby. (Pp. xi + 192; 167 figures; 45*s*.) London: Oxford University Press. 1960.

The author has been responsible for courses of lectures on perimetry, and this book is derived from those lectures. The author confines himself to the essentials of the subject, which are clearly expounded and simply illustrated. He has not added another to the detailed monographs on perimetry, but has provided an introduction to the subject giving a small selection of references for those who wish to pursue it further. It should prove a useful book to postgraduate students of neurology and ophthalmology.

American Handbook of Psychiatry, Vols. I and II. Edited by Silvano Arieti. (Pp. xxviii +2098; illustrated. £10. 0*s*. 0*d*.) New York: Basic Books; London: The Mayflower Publishing Co. 1959.

Edited under the leadership of Silvano Arieti by a board consisting of Kenneth E. Appel, Daniel Blain, Norman Cameron, Kurt Goldstein, and Lawrence C. Kolb, this is the first ever American 'compendium of the current state of knowledge in every branch of this rapidly advancing science'. It is 'offered as representative of American psychiatry today'. This claim 'refers specifically to the receptivity to all possible approaches which is characteristic of psychiatry in the United States' and accordingly the subject matter ranges more widely than most if not all other English language texts.

The work is made up of contributions by 111 authors (three of whom died while it was in preparation) which are grouped into fifteen parts and 100 chapters with 141 illustrations. Part 1 begins with a short historical sketch of American psychiatry up to World War II by Nolan D. C. Lewis, followed by 'recent American psychiatric developments' by G. Mora, and contains chapters by B. Malzberg on statistical data and F. J. Kallmann on the genetics of mental illness; unusually there are also chapters devoted to the family and the community of the psychiatric patient and one on psychiatric interviewing separate from the psychiatric examination, an excellent idea which could well have been extended. There follow more orthodox parts on the psychoneuroses and allied conditions; the functional psychoses (largely by the editor in chief); psychopathic conditions; psychosomatic medicine which curiously omits a chapter on skin diseases and the mind, but contains K. Goldstein on functional disturbance in brain damage; childhood and adolescence, including separate chapters on juvenile delinquency and reading and learning disabilities; part 7, which ends Volume I, devoted to 'language, speech, communications', is introduced by J. Ruesch on communication theory, has a chapter on stuttering, and ends with T. S. Szasz on language and pain.

Volume II opens with more than 200 pages devoted to the usual 'organic conditions' illustrated with small-scale gross and large-scale microscopic appearances of abnormal brains; then follow parts devoted to 'the psychotherapies'; a separate part on 'psychoanalytic therapies' (note the plural), and one on the physical therapies with contributions by L. B. Kalinowsky, W. Freeman, and P. H. Hoch. The remainder of the volume is made up of miscellaneous items. Part 12 on the 'relations with basic sciences and experimental psychiatry' has chapters on neuroanatomy (J. Papez), neurophysiology (R. W. Gerard), neurology (S. Cobb), neuropathology (L. Roizin), 'the biodynamic approaches' (J. H. Masserman), and pharmacologically induced psychoses (P. H. Hoch). Part 13 'contributions from related fields', deals with clinical and social psychology, mathematics and cybernetics, philosophy, and has chapters on psychiatric nursing, social work, and family care; and part 15 'legal, administrative, didactical, and preventive psychiatry', which naturally deals with these topics from the American standpoint, includes a chapter on forensic psychiatry by Winfred Overholser. Finally there is as complete an index as one could wish which runs to 111 pages. Each chapter has its own often extensive list of references: for instance that on neuropathology contains 280 items.

It is impossible to do justice to the enormous amount of information assembled in these volumes and the labour which must have gone into their making. In a work with so many contributors embracing a variety of disciplines and which attempts to be complete, some unevenness in standards is unavoidable. For example, statements like 'The nerve cell, with all its processes, is called a neuron', seem to be addressed to the laity, while few psychiatrists will be able to make out 'In discussing Vogt's pathoklisis . . . certain of the fundamental objections . . . could be overcome by the recently developed hypothesis of histometabolic dysergia'. Again a few contributions read as if their authors were trying to argue a case for their opinions and theories rather than giving a balanced and reasoned view, which may make it difficult for the beginner to form his own judgment. But this is perhaps due to the fact that psychiatry possesses a smaller body of knowledge derived from clinical observation and laboratory investigation than is generally realized; even much of everyday classification is subjective rather than objective and consequently uncertain and possibly ephemeral, quite apart from pathological formulations whether physical or psychological. Some chapters are

sufficiently complete to present a satisfactory expert view of their subjects against some which reach no higher level than that of a student's textbook.

Whether it is helpful theoretically or practically to regard schizophrenia, one of the central problems of psychiatry, as 'neurophysiologically . . . a process of functional dysencephalization', 'a disharmony of microscopic spatiotemporal patterns of activity in the neuronal network' only the future can decide. But such statements do show that psychiatry is in a state of uncertainty and flux and seeking help from an ever widening circle of ancillary disciplines. In the circumstances only a brave man would attempt a systematic presentation while there is so little fundamental knowledge to systematize. Dr. Arieti and his coeditors have sought to overcome this difficulty by opening their pages to representatives of all schools and approaches. Casting their net so widely has resulted in two unwieldy volumes which together weigh 10 lb. However, the student who invests in them at 20*s.* the pound is assured of much valuable material and will be reassured that mid-twentieth century psychiatry does not lack inventiveness of theory to overcome a shortage of fact.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Mental Symptoms in Temporal Lobe Epilepsy and Temporal Lobe Gliomas [*Acta psychiat.* (*Kbh.*), Suppl. 120, Vol. 33, 1958.] Copenhagen: Ejnar Munksgaard.

Papers on Hemiballismus and the Basal Ganglia (1927-1960). By J. Purdon Martin. (Pp. 60. 7*s.* 6*d.*) London: H. K. Lewis. 1960.

The Electrical Activity of the Nervous System, 2nd ed. By Mary A. B. Brazier. (Pp. 273. 35*s.*) London: Pitman Medical Publishing Co. 1960.

Felduntersuchungen über Multiple Sklerose in Unterfranken: Eine Studie an 110 Patienten in 46 Gemeinden. By Hans Georg Bammer; Foreword by G. Schaltenbrand. (Pp. viii + 103; 44 figures, 10 tables. DM 15.-.) Stuttgart: Georg Thieme. 1960.

The Unconscious Before Freud. By Lancelot Law Whyte. (Pp. xiii + 219. $4.50.) New York: Basic Books. 1960.

Intraspinal Tumors of Childhood. By Robert W. Rand and Carl W. Rand. (Pp. xvii + 560; 34 colour plates, 245 figures. £6. 12*s.*) Oxford: Blackwell; Springfield, Illinois: Thomas. 1960.

Electrical Studies on the Unanesthetized Brain. Edited by Estelle R. Ramey and Desmond S. O'Doherty. (Pp. xiii + 423; 224 figures. $6.00.) New York: Paul B. Hoeber. 1960.

An Introduction to Psychoanalytic Research. By Kenneth Mark Colby. (Pp. ix + 117. $3.00.) New York: Basic Books. 1960.

Les Compressions de la Moelle Cervicale: Lésions Intrinsèques et Traumatiques Exclues. By L. Ectors, J. Achslogh, and M. J. Saintes. (Pp. 164; 37 figures. NF 28.-.) Paris: Masson & Cie. 1960.

Les Abcès Encéphaliques a L'ère des Antibiotiques: Étude Statistique de 547 Observations. By J. Bonnal, P. Descuns, and J. Duplay. (Pp. 154; 9 figures and 30 tables. NF 26.-.) Paris: Masson & Cie. 1960.

La Radiculographie Lombaire dans la Sciatique. By J. Ecoiffier. (Pp. 140; 37 figures and 51 plates. NF 40.-.) Paris: Masson & Cie. 1960.

Seventh International Congress of Neurology and Fifth International Congress of Electroencephalography and Clinical Neurophysiology

The Seventh International Congress of Neurology will be held in Rome, September 10-15, 1961.

Topics for September 11 are "Neurologic disorders in porphyria, phenylketonuria, and galactosuria" (morning) and "Neurologic disorders related to liver diseases" (afternoon); for September 12 "Brain disturbances associated with cardiopulmonary disorders"; for September 14 "Aphasia".

Symposia will be concerned with "Lipids, Lipoproteins and their Metabolism" and with "Changes in Myelin" on September 13. A symposium on neurological genetics will be held on September 10 in the morning jointly with the Third International Conference of Genetics (Rome, September 7-12, 1961). The other symposia will deal with neurological geography, history of neurology, and multiple sclerosis.

September 15 will be devoted to the communications on major topics and to free communications.

Registration fees are $15.00 (or equivalent in Italian lire) for active members; $10.00 for associate members, $5.00 for adjunct members.

All information from Dr. Giovanni Alema, Viale Università 30, Rome. For the symposium on neurochemistry, information from Dr. Armand Lowenthal, Secretary for Neurochemistry, within the World Federation of Neurology, 59, rue Philippe Williot, Berchem-Anvers (Belgium); for the symposium on neurological genetics, from Prof. Luigi Gedda, Istituto Gregorio Mendel, Piazza Galeno 5, Rome.

The V international congress of electroencephalography and clinical neurophysiology will be held from September 7 to 13, 1961. The topics for September 7 are "Relation between unit activity and electroencephalogram" (morning), and "E.E.G. in phylogenetics", "Diffuse projection systems to cortex and their function according to animal species and cortical organization", and "E.E.G. and sleep" (afternoon). On September 8 a round table will be held on "Intracerebral electrography in man". In the afternoon G. F. Ricci and R. Hernandez-Peon will submit a report on "E.E.G. and physiology of behaviour" and G. G. Walter and Storm van Leeuwen on "The analysis of E.E.G. information". On September 9 the topic "E.E.G. of non-epileptic paroxismal disturbances" will be presented in the morning.

September 16 is devoted to the meeting of the International League against Epilepsy in the morning and will deal exclusively with "Epilepsy in childhood".

September 11 and 12 are reserved for the joint meetings with the VII International Congress of Neurology, and September 13 is reserved for communications.

Registration and other fees are the same as those for the Congress of Neurology. All information from Dr. Raffaello Vizioli, Viale Università 30, Roma.

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INTRATHECAL TUBERCULIN IN DISSEMINATED SCLEROSIS: THE IMMUNOLOGICAL ASPECTS

BY

HONOR V. SMITH, IWAN E. HUGHES,* and GEORGE HUNTER*

From the Department of Neurology, the United Oxford Hospitals

Four years ago a preliminary report was published on the intrathecal injection of the purified protein derivative of tuberculin (P.P.D.) in disseminated sclerosis (Smith, Espir, Whitty, and Russell, 1957). In someone sensitized to tuberculin, whether as a result of natural infection or of vaccination, these injections provoke a wave of meningitis which is the expression of a true, specific allergic reaction (Swithinbank, Smith, and Vollum, 1953). It has been suggested that, in disseminated sclerosis, an alteration in formation and flow of the cerebrospinal fluid (C.S.F.) and of the blood-cerebrospinal fluid barrier, such as occurs in meningitis, might influence the course of the disease for the better (Bourdillon, Fischer-Williams, Smith, and Taylor, 1957). The intrathecal injection of P.P.D. is the least objectionable way of setting up a meningitis, since the reactions are sterile and self-limiting, and experience gained in treating tuberculous meningitis has shown that it is possible to evolve a scheme of dosage which minimizes the dangers (Smith, Vollum, Taylor, and Taylor, 1956). Further, the reactions markedly and constantly increase the permeability of the blood-C.S.F. barrier (Smith, Taylor, L. M., and Hunter, 1955). Further, these reactions offer a direct method for testing once again the well-known hypothesis that hyperaemia of the neuraxia would be beneficial, since animal experiment has shown that the inflammation is not limited to the leptomeninges but also involves the perforating vessles of the brain-stem (Bosanquet, Daniel, and Vollum, 1953). For these reasons volunteers for this hitherto untried form of treatment were sought from amongst our most severely affected patients.

In the event this method of treatment proved to have yet another advantage. Ever since tuberculin was first prepared (Koch, 1890) its antigenic properties have been studied intensively, both in the field and in the laboratory, and its name has been given to one main kind of allergy, the "delayed" or "tuberculin type" of sensitivity. Its intradermal and intrathecal use in disseminated sclerosis has therefore provided data for a study of the "delayed" type of immune response in this disease.

In our preliminary report we described the intrathecal reactions in disseminated sclerosis and showed that they differed markedly and consistently in pattern from those seen in cases of different kinds of psychosis. Reasons were given for accepting the latter as exemplifying the normal, and it was concluded that the distortion of pattern seen in disseminated sclerosis was evidence of an immunological disturbance in that disease. This conclusion was supported by the finding that certain tuberculin-negative patients proved surprisingly refractory to vaccination with B.C.G. or Wells' vole bacillus vaccine (W.V.V.). Finally, the hope that these reactions might have a therapeutic value was encouraged by the fact that, at the time when our report was published, no patient had relapsed or continued to grow worse since treatment (Smith *et al.*, 1957).

Many patients did, indeed, improve. Without making any claims to a causal relationship between treatment and improvement, it was at least clear that the reactions neither prevented nor delayed remission. This being so, we steadily expanded this study until, at the present time, over 280 patients have been treated. The immunological aspects of this work are considered here and later, in a separate clinical paper, an attempt will be made to evaluate the therapeutic possibilities.

Clinical Material

Patients were recruited from among those attending the Department of Neurology of the United Oxford Hospitals, or were referred to us from elsewhere for the purpose of this study. Care was always taken to explain that this attempt at treatment was a research project and that, as such, its therapeutic value was not established; that it was not free from risk; and that its aim was to delay

*Working with a grant from the Nuffield Foundation.

further deterioration or relapse rather than to restore function.

The present study is limited to 248 cases in which, on clinical grounds, the diagnosis was reasonably certain. Cases are excluded in which some complicating factor, such as cervical spondylosis, was suspected, or in which the laboratory data are incomplete. The basis on which cases were selected for treatment, and on which the diagnosis was accepted, is discussed in the clinical paper.

Sex Incidence.—One hundred and five patients were males and 143 females. This ratio of 1 : 1·38 is of the same order as in other published series (McAlpine, Compston, and Lumsden, 1955; McAlpine, 1961) and almost certainly reflects a true excess of women, at least in this country. This conclusion is strengthened by the fact that, while we have approximately equal hospital accommodation for either sex, we have, from the beginning of this study, laboured under a heavy waiting list for women while that for men has never been a problem.

Age Incidence.—The distribution of patients according to age at time of treatment is shown in Table I. The peak incidence, with 45·5% of cases, is in the fourth decade of life. The comparative rarity of patients over 50 years old or under 20 is because, on the one hand, we are reluctant to submit the older patient to such a strenuous form of treatment, while on the other, we insist that there should have been at least two well-marked episodes in the illness before admitting anyone for treatment.

TABLE I

AGE INCIDENCE AT TIME OF TREATMENT

Age (years)	Total	Males	Females
	No.	No.	No.
Under 20	12 (5%)	6 (6%)	6 (4%)
20-29	46 (18·5%)	17 (16%)	29 (20%)
30-39	113 (45·5%)	46 (44%)	67 (47%)
40-49	63 (25%)	29 (28%)	34 (24%)
50 and over	14 (5%)	7 (6%)	7 (5%)
Total	248	105	143

The men tended to be slightly older than the women but the difference is not significant. The mean age for men is 35·9 years and the range from 16 to 60, while for women the mean is 35·3 years with a range of from 14 to 57. For both sexes there is a well marked peak in the third decade (Fig. 1).

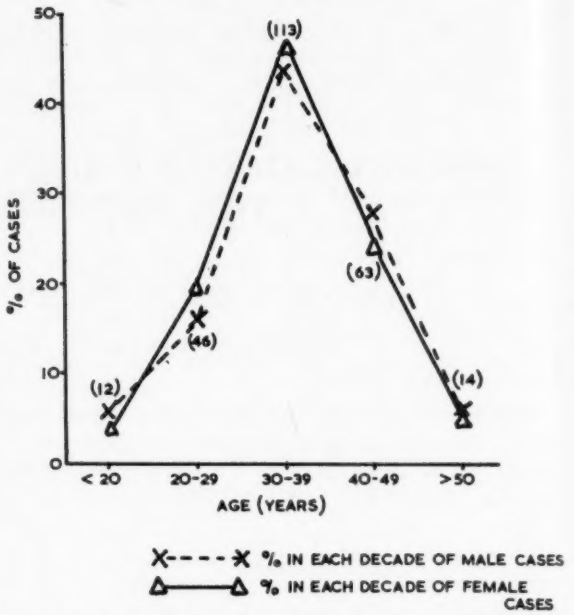

FIG. 1.—The percentage of total males and females in each decade of life at time of treatment. The figures in brackets show the total number of cases in each age group. The distribution according to age is essentially the same for both sexes.

TABLE II

DURATION OF ILLNESS AT TIME OF TREATMENT

Duration of Illness	Total	Males in Each Group
		No.
1 yr. and under	30	14 (47%)
1 yr. 1 mth. to 3 yr.	48	16 (33%)
3 yr. 1 mth. to 5 yr.	40	16 (40%)
5 yr. 1 mth. to 7 yr.	42	14 (33%)
8 yr. to 10 yr.	37	17 (46%)
11 yr. to 15 yr.	29	17 (59%)
Over 15 yr.	22	11 (50%)
Total	248	105 (42·3%)

Duration of the Illness.—Table II shows the duration of the illness at the time of treatment for both sexes. There are rather more than the expected number of males among those in whom the duration exceeded seven years. The difference just falls short of conventional significance at the 5% level. When, however, the cases of natural conversion (*vide infra*) are considered alone, the difference achieves significance.

Clinical Classification.—It is characteristic of disseminated sclerosis that the pattern of the illness should vary widely from case to case. In an attempt to meet some of the difficulties that this imposes we have used the following classification, derived from published statistical studies of the disease, notably that of Müller (1949).

Cases are divided into five groups, according to the pattern of the illness at the time of treatment, thus:

A (i) *Relapsing-Remitting.*—This group is made up of those cases in which the illness is running a relasping, remitting course, and in which the duration

does not exceed five years. For inclusion no sign or symptom must have grown worse for more than one year. It follows that all cases in which the total duration of the illness is less than one year fall automatically into this group.

A (ii) *Relapsing-Remitting, Duration More than Five Years.*—This group consists of those cases in which relapses and remissions are still occurring although the duration of the illness exceeds five years. As in A (i) progression of any symptom for more than one year excludes.

B (i) *Progressive.*—For inclusion in this group the duration of the illness must exceed one year and there must have been no sustained improvement of any sign or symptom at any time. Even a stationary phase for as long as three months excludes.

B (ii) *Progressive Except for Remission of a Retrobulbar Neuritis.*—The criteria are the same as for B (i), except that the history includes an attack of retrobulbar neuritis with subsequent improvement in vision.

C Relapsing-Progressive.—This group is made up of the cases in which the earlier pattern of relapses and remissions has given place to one of steady progression. For inclusion at least one sign or symptom must have grown steadily worse for more than one year.

The arbitrary choice of one year for use in these definitions is based on Müller's finding that spontaneous remission, and in this he includes a stationary phase, occurs in only 6% of cases in which symptoms have progressed for one year. Since he and others have shown that the interval between relapse increases with the duration of the illness, especially after this has reached five years, it follows that the expectation of relapse is highest in group A (i) and the expectation of remission lowest in group B (i) and (ii). This classification is further discussed in the clinical section.

Table III shows the cases in the present series classified in this way. The relative frequencies of the different groups are, almost certainly, not representative of the natural distribution since, when selecting patients for treatment, we have given preference to those belonging to groups A (i) and B (i) and (ii). Nevertheless group C, the relapsing-progressive, remains the largest, reflecting the well-marked tendency for the disease, sooner or later, to become progressive.

TABLE III

CLASSIFICATION OF PRESENT SERIES

	Number of Cases	% of Total
A (i) Relapsing-remitting	74	30
A (ii) Relapsing-remitting duration over 5 years	32	13
B (i) Progressive	47	19
B (ii) Progressive except for retrobulbar neuritis	17	7
C Relapsing-progressive	78	31
Total	248	100

Methods of Study

The material for this study was derived from the results of the Mantoux tests; from the results of vaccination where the Mantoux test was negative; from a study of the C.S.F. during the reaction; and from the progress of the illness during the following year.

The Mantoux Test.—Serial Mantoux tests were done in the usual way using 1/10,000, 1/1,000, and 1/100 dilutions of old tuberculin. Sometimes the 1/10,000 dilution was accidentally omitted. The site of injection was inspected at 24 hours and the test read at 48 hours. The minimal requirement for a positive result was an area of induration measuring not less than 10 mm. in diameter.

Vaccination.—When the Mantoux test was negative to old tuberculin 1/100 the patient was vaccinated either with Wells' vole bacillus vaccine (W.V.V.), or B.C.G., or first one and then the other.

Vaccination with W.V.V. was carried out by Dr. R. V. Vollum by the multiple puncture technique. If conversion was not obtained within a reasonable time this was repeated. Certain patients, who proved highly resistant, were vaccinated a third time with 0·1 mg. given by intradermal injection. Both fresh and freeze-dried vaccines were used.

B.C.G. vaccination was carried out at the chest clinic most conveniently situated for the patient. Again both fresh and freeze-dried vaccine were used.

Following vaccination the Mantoux test to old tuberculin 1/100 was carried out as often as was practicable. If conversion was not obtained in two or three months the patient was re-vaccinated. As soon as possible after conversion the patient was admitted for treatment.

Examination of the C.S.F.—The normal intrathecal tuberculin reaction, when fully developed, is diphasic. The cell counts show two well-marked peaks, one occurring 24 hours, and the other five to eight days after the injection. The protein content tends to follow the same pattern as does the increase in permeability of the blood-C.S.F. barrier as shown by the bromide test (Swithinbank *et al.*, 1953; Smith *et al.*, 1955). The C.S.F. examinations were accordingly timed to cover both phases of the reaction.

Soon after admission a diagnostic tap was performed. Cell counts and protein estimations were done and often the Lange curve was determined. In some cases, especially towards the latter part of this study, the protein of the C.S.F., and sometimes of the serum, was fractionated with particular reference to the globulin fraction. At first the immunological method of Kabat, Glusman, and Knaub (1948) was used but later this was superseded by electrophoresis (Sheff and Mynors, in preparation).

At least two days before the first injection of P.P.D. 2 g. sodium bromide was given by mouth. Lumbar puncture was repeated on the first and either the fifth or sixth day after intrathecal injection of P.P.D., and in some cases more often. After the definitive reaction the C.S.F. was examined at intervals until the patients' discharge from hospital. When possible 5 to 10 ml. C.S.F. was collected at each tap in two separate portions. From 5 to 10 ml. of blood was collected in a dry tube at the same time as each spinal tap Total and differential white cell counts were done. The protein content was estimated nephelometrically and in duplicate, once in the clinical laboratory of the hospital where the patient was, and again by one of us (G.H.). Cases in which there was a significant discrepancy between the results of the estimations have been excluded from this study. The red cells were also counted in each specimen, since contamination with blood is a potent source of error in C.S.F. protein determination and in cell count. The bromide content of both serum and C.S.F. was estimated (Hunter, 1955) and the results expressed as the bromide ratio, *i.e.*, C.S.F. bromide: serum bromide.

Intrathecal Dosage of P.P.D.—The hazards of intrathecal P.P.D. and the clinical events accompanying the reaction will be described in the clinical section. The aim of treatment is to produce the maximal changes in the C.S.F. compatible with safety. Experience has shown that if the injection of P.P.D. is repeated before the effects of the previous injection have subsided, that is to say, during the second phase of the previous reaction, the reaction to the second injection is often greatly enhanced even though the dose is kept the same. This helps to increase the margin of safety. The result of the Mantoux test is no guide to dosage since, by contrast with the findings in tuberculous meningitis and in the psychotic patients, there is no apparent correlation in cases of disseminated sclerosis between the intensity of the intradermal and that of the intrathecal reactions. Vaccinated patients have, however, proved much more tolerant to intrathecal P.P.D. than those in whom the Mantoux test converted naturally.

The following scheme of dosage has proved practicable. The P.P.D. is obtained from the Ministry of Agriculture Research Laboratories, Weybridge, and diluted with normal saline to a solution containing 7·5 μg. per ml. This is known as the "standard" (ST) solution. This is then diluted tenfold to form the ST/10 solution. Except in a few early cases higher dilutions than this have not been used. The first dose given is 0·5 ml. ST/10, *i.e.*, 0·375 μg. The size of the second dose depends on the severity of the reaction to the first, but does not exceed 2·5 ml. ST/10 (1·875 μg.). Rarely, a third dose of 0·5 ml. ST (3·75 μg.) is given. In vaccinated cases the initial dose is usually 2·5 ml. ST/10 (1·875 μg.), and 0·5 ml. ST (3·75 μg.) and even 1·0 ml. ST (7·5 μg.) may be given as the second and third doses.

Results of the Mantoux Test

Table IV shows the results of the Mantoux test in 248 cases. In 103 cases, or 41·9% of the total, the test was positive to O.T. 1/1,000. This incidence is almost certainly a little too high, and that of 15·4% for positive reactions to O.T. 1/10,000 a little too low, as not everyone who proved positive to the lower dilution was also tested with the higher.

TABLE IV
RESULTS OF MANTOUX TEST

Mantoux Test Positive to O.T.	Age (years)					Total	% of Series
	<20	21-30	31-40	41-50	51 and over		
1:10,000	1	10	15	10	2	38	15
1:1,000	4	10	51	31	7	103	42
1:100	0	9	25	14	4	52	21
Mantoux Test Negative							
1:100	7	17	22	8	1	55	22

In 55 cases, 22·4% of the series, the test was negative to O.T. 1/100. How this incidence compares with that of the population as a whole is not known. In this series there is considerably variation as to age and social status; it includes both urban and rural dwellers. This variation has made it impossible to find a comparable series among the many published tuberculin surveys. Unquestionably, a fair number of tuberculin-negative cases is to be expected, since disseminated sclerosis affects young people. But, as Table IV shows, our Mantoux-negative cases, though relatively more common among those in the second and third decades of life, are by no means confined to this age group. Thirty-one of the patients, or well over one half, were over 30 years old and nine were over 40. In these 55 cases tuberculin sensitivity was conferred artificially. They are, therefore, in many respects most conveniently treated as a separate group. In this study they are called the "vaccinated" to distinguish them from the "natural conversions".

Effect of Sex on Intradermal Sensitivity.—In Great Britain, the older the individual, the more likely he is to be infected with *M. tuberculosis* and so to become tuberculin positive. The incidence of tuberculin sensitivity in any given population is, therefore, largely determined by the age distribution within that population. Further, for any given age group, the incidence of tuberculin sensitivity, and therefore presumably, the risk of exposure is about the same for the two sexes. Nor is the intensity of the reaction normally affected by the sex of the patient as shown by Griep and Bleiker (1957) in their careful quantitative study of the intradermal tuberculin test. Our experience with cases of tuberculous meningitis is the same. In this disease tuberculin sensitivity is commonly depressed and may even be abolished (Taylor, L. M., Smith, and Vollum,

1953). Table V shows the results of serial Mantoux tests carried out in 50 adolescents and adults with tuberculous meningitis. There is clearly no difference whatever between the sexes.

TABLE V

RESULTS OF MANTOUX TESTS IN CASES OF TUBERCULOUS MENINGITIS

Mantoux Test Positive to O.T.	Total No. of Cases	No. of Males
1/10,000	10	5 (50%)
1/1,000	24	12 (50%)
1/100	13	6 (46%)
Mantoux Test Negative		
1/100	3	2 (67%)
Total	50	25 (50%)

In our cases of disseminated sclerosis, however, the position is very different. The mean age and age distribution for the two sexes is much the same and therefore the proportion of Mantoux-negative cases should also be the same. But, in point of fact, 42, or 30%, of the women were Mantoux negative, and only 13, or 12·5%, of the men. This difference is significant at the 1% level.

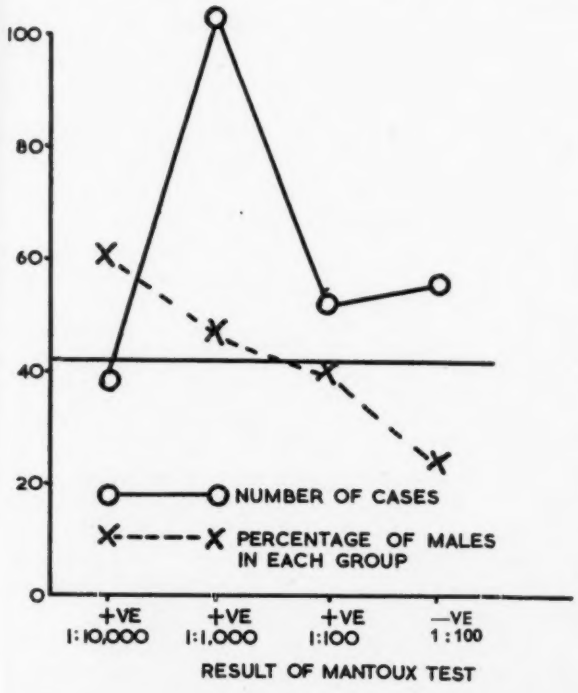

FIG. 2.—The number of cases plotted against Mantoux status, together with the percentage of males in each separate group. The percentage of males falls progressively as tuberculin sensitivity declines. The horizontal line shows the expected percentage of males, *i.e.*, the percentage in the series as a whole.

TABLE VI

RESULTS OF MANTOUX TESTS IN CASES OF DISSEMINATED SCLEROSIS

Mantoux Test Positive to O.T.	Total No. of Cases	No. of Males
1/10,000	38	23 (60·5%)
1/1,000	103	48 (46·6%)
1/100	52	21 (40·4%)
Mantoux Test Negative		
1/100	55	13 (23·6%)
Total	248	105 (42·3%)

Further, when the cases are divided into four groups according to the result of the Mantoux test, and the distribution of the sexes studied within each group, the proportion of males is seen to decline progressively with the decrease in sensitivity (Fig. 2 and Table VI). Thus, at the two extremes, of the 38 in whom the test was positive to O.T. 1/10,000, 23, or 60·5%, were males; while in the 55 in whom the test was negative only 13, or 23·6%, were males. This difference is also significant. (The value for χ^2 was calculated, allowing for continuity, $\chi^2=8{\cdot}426$ (d.f.=1); $0{\cdot}01>P>0{\cdot}001$.)

In this series, therefore, the males are significantly more sensitive to tuberculin than are the females.

The Response to Vaccination

The observation made in our earlier paper (Smith *et al.*, 1957) that some tuberculin-negative patients were surprisingly refractory to vaccination, has now received ample confirmation. Unfortunately, in a fair number of cases the full history of Mantoux conversion, and possible reversion, is not known as the patients lived far away: they were vaccinated near their homes and after discharge from hospital were not available for re-testing. However, we have been able to make enough observations for it to be abundantly clear that the response to vaccination was abnormal in a considerable proportion of cases.

The chief abnormalities noted have been delayed or incomplete conversion, the patients not infrequently requiring re-vaccination; and a high reversion rate. In addition, the degree of sensitivity conferred has been low in that in the great majority of cases the Mantoux test has only become positive to O.T. 1/100.

Conversion Time.—This is best studied in those patients vaccinated with W.V.V. As a research tool W.V.V. has the advantage of being a natural strain of murine tubercle bacilli not attenuated artificially. Further, the conversion rate is very high, the reversion rate low, and conversion takes

place rapidly. Thus Hall and Wylie (1952) obtained 100% conversion within four weeks in a group of 33 children attending a special school.

Of the 27 patients vaccinated with W.V.V., the conversion time is known in 20, in 12 it was significantly prolonged beyond four weeks, six had to be re-vaccinated, and in three full conversion was not obtained in spite of repeated vaccinations.

Such information as we have about the time of conversion in our patients after B.C.G. vaccination indicates that delay was equally common; certainly re-vaccination was frequently required.

Reversion of the Mantoux Test.—Unfortunately, only nine patients have been retested after conversion to W.V.V. Four of these were found to be again tuberculin negative. Once again, the reversion appears to be at least as common after vaccination with B.C.G. as with W.V.V.

Finally, reversion to the negative state after natural conversion has been seen in three, possibly four cases; and in another two, in which the Mantoux test was negative, a radiograph of the chest showed calcification typical of an old tuberculous primary complex.

Since these figures really give little idea of the bizarre response to vaccination, short notes of some representative cases are appended.

Case 1 (No. 236): Slow Conversion with Rapid Reversion.—A woman of 37 had been ill for four and a half years during which time her symptoms had progressed slowly but without remission (clinical group B (i)). Her general condition was excellent and her disability mild. Eight weeks after vaccination with W.V.V. the Mantoux test was still negative and she was accordingly re-vaccinated. After a further eight weeks the test was still negative nor was either vaccination site detectable. She was accordingly re-vaccinated with 0·1 mg. of lyophilized vaccine given by a single intradermal injection. Three months later she had a small ulcer at the third vaccination site and the Mantoux test was positive. She was then treated with intrathecal P.P.D. Nine months later the ulcer was firmly healed and the Mantoux test was once again negative. Her neurological condition was unchanged. All Mantoux tests were done with O.T. 1/100.

Case 2 (No. 88): Normal Conversion with Reversion.—Slow conversion after vaccination was followed again by reversion.

A trained nurse of 24 years had been vaccinated with B.C.G. when she entered her training school six years earlier. The Mantoux test had converted rapidly and was still positive to O.T. 1/100 when she was first seen by us. She had by then been ill for one and a half years during which time the disease had run an increasingly rapid, progressive course without remission (clinical group B (i)) to the point where she was badly disabled by a spastic ataxic paraparesis and severe frequency of micturition.

Following treatment with intrathecal P.P.D. she had an excellent remission and returned to nursing. Eighteen months later she had a severe relapse and was admitted for re-treatment. The Mantoux test was now found to be negative. She was then vaccinated with W.V.V. and, as conversion was not obtained, was vaccinated with 0·1 mg. lyophilized vaccine. This time the Mantoux test did convert and accordingly she was re-treated. Her recovery from the reaction was delayed by an attack of lobar pneumonia but at the present time, one year later, she is again in remission, though with a moderate residual paraparesis, and the Mantoux test has once again become negative.

Case 3 (No. 171): Reversion after Natural Conversion.—Failure to reconvert after vaccination.

A woman of 42, who had been ill for seven years and in whom the disease had at first remitted and then entered the progressive phase (clinical group C), was severely disabled by generalized ataxia, a moderate spastic paraparesis, and gross dementia. The Mantoux test was positive to O.T. 1/100. The reactions obtained to even very large intrathecal doses of P.P.D. were most disappointing and accordingly she was vaccinated with W.V.V. in an attempt to increase the sensitivity to tuberculin. One week later the Mantoux test was found to be negative and it remained so in spite of a further vaccination. Following treatment she improved a little, both physically and mentally, but relapsed nine months later. Her present Mantoux status is unknown.

What it is in these patients that prevents tuberculin sensitivity of the skin from developing in the normal way is not known. The low conversion and high reversion rates are reminiscent of the findings in sarcoidosis but, by contrast with Scadding's findings in that condition (Citron and Scadding, 1957), injecting cortisone with the tuberculin had no detectable effect on the result.

Close scrutiny of the site of the intradermal injection often gives the impression that the reaction begins to develop normally and is then aborted. Thus it is not uncommon to find a well-marked flare, and even a little early induration, 24 hours after the injection; but then, when the test is read at 48 hours, all signs of a reaction have disappeared. In a few patients, in whom the intrathecal response was negligible, the C.S.F. was examined at 12 as well as at 24 hours after the injection of P.P.D., with rather similar results. The 12-hour specimens have contained many hundreds of cells per c.mm., the great majority of which have disappeared from the 24-hourly specimen.

The relationship between the development of this immunological abnormality and the evolution of the disease is also obscure. Such information as we have, however, suggests that, so far from antedating it, the abnormality develops as the disease advances. Thus, in Case 3 Mantoux conversion before the development of disseminated sclerosis

appears to have been perfectly normal, and in several of our cases the first vaccination produced prompt and satisfactory conversion to be followed a few years later by reversion and by marked resistance to vaccination. Nor have we found any obvious relationship between reversion of the Mantoux test and the onset of relapse. It is true that many of those patients in whom the test was found to have reverted were in relapse, but it was the relapse that led to their re-admission, and therefore gave us the opportunity of re-testing them, and we know of at least one patient in whom the Mantoux test has reverted and in whom, nevertheless, the progressive phase of the disease has been interrupted by an excellent remission.

An attempt is made below to determine whether or not this abnormality can be related to any particular clinical feature of the illness.

Clinical Differences between Vaccinated and Natural Conversions.—It follows from what has been said that, in all probability, the vaccinated must form a mixed group made up, on the one hand, of those who have never been infected with *M. tuberculosis* and, on the other, of those who, having been infected, were either not sensitized or else lost their sensitivity. As Table IV shows, the proportion of young patients is rather larger among the vaccinated than in those with natural conversions. For the rest, the only difference we have found is in the distribution of the clinical groups.

Table VII shows the natural conversions and the vaccinated divided into the different clinical groups. The total number of the natural conversions divided by that of the vaccinated gives a ratio of 3·5. If the distribution of the groups were uniform then this should be the ratio in each separate group. In fact, this is so for the two classical groups, that is to say, for the young relapsing-remitting cases (A (i)) and the relapsing progressives (C). For the rest, the ratio for the long-term relapsing cases (A (ii)) is too small while for the steadily progressives (B (i) and (ii)) it is too large.

TABLE VII

CLASSIFICATION OF NATURAL CONVERSIONS AND VACCINATED

	A (i) No.	A (ii) No.	B (i)+(ii) No.	C No.	Total
Natural conversion	58 (30%)	20 (10%)	53 (27%)	62 (32%)	193
Vaccinated	16 (29%)	12 (22%)	11 (20%)	16 (29%)	55
Ratio Nat. conv./ vaccinated	3·5	1·66	4·8	3·9	3·5

This finding suggests that among the vaccinated there is a greater tendency to remit than among the natural conversions, in that rather more patients have retained the capacity to remit for more than five years while in rather fewer the disease had run a relentlessly progressive course from the outset.

The Intrathecal Reaction

In our earlier paper it was shown that the major departure of the pattern of the reaction in disseminated sclerosis from that of the normal was that the first phase of the reaction failed to develop properly, largely because the expected number of polymorphonuclear leucocytes did not appear in the C.S.F. In addition, taking the reaction as a whole, the rise in the protein content was remarkably high, particularly in conjunction with the low cell counts. Both these anomalies may now be examined in more detail.

The First Phase of the Reaction

For the purposes of this study the first phase of the reaction is defined as the changes in the C.S.F. 24 hours after an injection of P.P.D.

Cell Counts.—In the psychotic cases the most constant feature of the reaction was a well-marked pleocytosis, with a high percentage of polymorphonuclear leucocytosis, 24 hours after the injection of P.P.D. when counts of 1,000 or more cells per c.mm. were common (Swithinbank *et al.*, 1953). In cases of tuberculous meningitis a similar sharp rise in the cell count is the rule. Fig. 3 shows the distribution of the cell counts 24 hours after P.P.D. in 50 cases of tuberculous meningitis.

All patients were adolescent or adult. When several doses of P.P.D. were given the reaction showing the highest cell count at 24 hours was chosen. The dose of P.P.D. varied widely from case to case but, as in the cases of disseminated sclerosis, the aim was to produce the greatest changes in the C.S.F. compatible with safety. The tendency towards high cell counts is obvious, and in 29 cases, or well over one half, 1,000 or more cells per c.mm. were present.

In Fig. 4 the 24-hourly cell counts in the 248 cases of disseminated sclerosis are set out in the same way.

The findings in the natural conversions are shown above the line and in the vaccinated below. As in the cases of tuberculous meningitis, when several doses of P.P.D. were given the most severe reaction was chosen. Among these natural conversions, where the cell count was 100 or less per c.mm., are several early cases in which very small doses of P.P.D. were given. For the rest, the principle of dosage was to produce the briskest reaction compatible with safety.

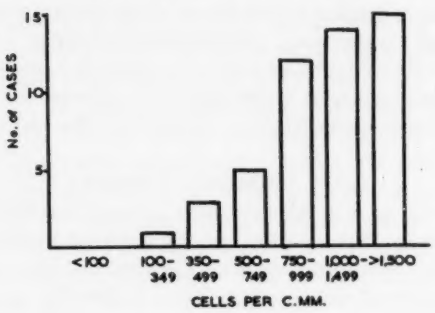

FIG. 3.—Histogram showing the distribution of 50 cases of tuberculous meningitis (children excluded) according to the cell count in the C.S.F. 24 hours after P.P.D. The incidence rises smoothly to a peak at 1,500 cells or more per c.mm.

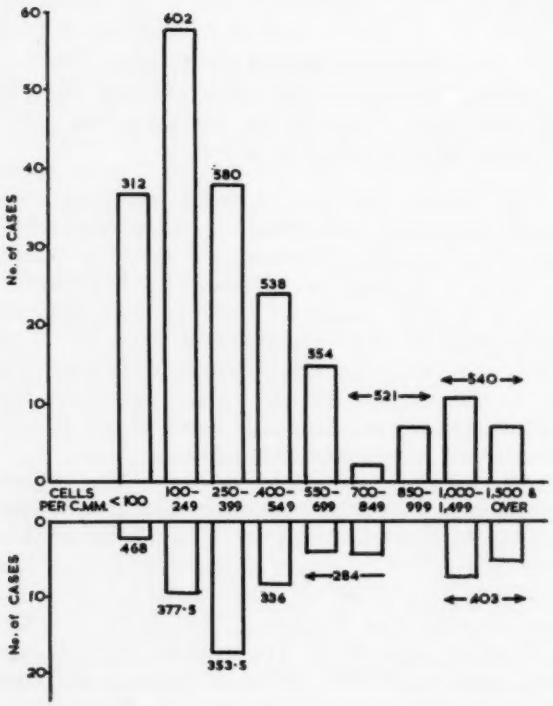

FIG. 4.—Similar histogram to that in Fig. 3, but for the cases of disseminated sclerosis. The natural conversions are plotted above the line and the vaccinated below. The figures above each column show the mean values of the protein content in the cases comprising each column.

The distribution is quite different from that in Fig. 3; both above and below the line the incidence shows a double peak, a high one among the low cell counts, and a second, much smaller one at counts of 1,000 cells and more per c.mm.

Throughout the low-cell cases the mean protein varies inversely with the cell counts and is much higher for the natural conversions than for the vaccinated.

The distribution of the cell counts contrasts sharply with that in the cases of tuberculous meningitis. Among the natural conversions the incidence shows a sharp peak at the 100 to 249 range and then declines smoothly to the range of from 700 to 849 where there are only two cases. At this point, however, the decline stops and the incidence again increases to a second, smaller peak at the 1,000 to 1,500 range.

A very similar distribution is seen among the vaccinated. Once again, the incidence declines from a well-marked peak to zero, and once again this decline is reversed by a second group of cases in which the C.S.F. contained 1,000 cells or more per c.mm. On the whole, the cell counts among the vaccinated tend to be higher than among the natural conversions. The peak incidence lies to the right of that for the natural conversions while the percentage of cases with cells of 1,000 or more per c.mm. is higher (20% as compared with 9·2%). This difference, however, falls short of conventional significance.

Thus in 18, or 9·2%, of the natural conversions, and in 11, or 20%, of the vaccinated, that is to say, in 11·7% of all cases, the C.S.F. contained 1,000 or more cells per c.mm. Differential cell counts show that the high total counts are largely due to the numbers of polymorphonuclear leucocytes present. These cases are too numerous, and their occurrence among the natural conversions and the vaccinated too constant, for them to represent merely a chance fluctuation on the distribution curve. Scrutiny of the histories and clinical findings in these cases leaves little doubt that the diagnosis was correct; certainly the criteria for diagnosis were applied at least as stringently as in the rest.

It appears, therefore, that this series is not homogeneous but consists of two separate groups: one, the large majority, in which the cellular component of the first phase fails to develop properly; and the other, a small minority, in which it approximates to the normal. This conclusion is also supported by study of the individual case. When, as has sometimes happened, two or even three separate courses of P.P.D. have been given, the pattern of the reaction has proved remarkably constant for the individual.

Taking 1,000 cells per c.mm. as the dividing mark, we find it convenient to speak of the majority as the "low-cell group" and of the minority as the "high-cell" group.

Specificity of Findings for Disseminated Sclerosis.—To what extent these findings are specific to disseminated sclerosis is not yet established. With very few exceptions our own experience with P.P.D. is limited to psychoses of various kinds, to tuberculous meningitis, and to disseminated sclerosis itself. Marshall and O'Grady (1959), however, have published data which go some way towards filling this

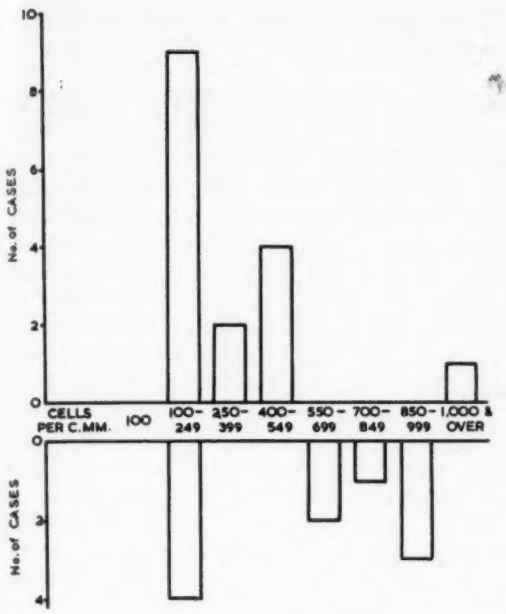

FIG. 5.—Similar histogram to that in Fig. 4, but for the data for Marshall and O'Grady (1959). The cases of disseminated sclerosis are plotted above the line and the controls below. The distribution of the cases of disseminated sclerosis is essentially the same as that in Fig. 4 and differs significantly from that of the controls.

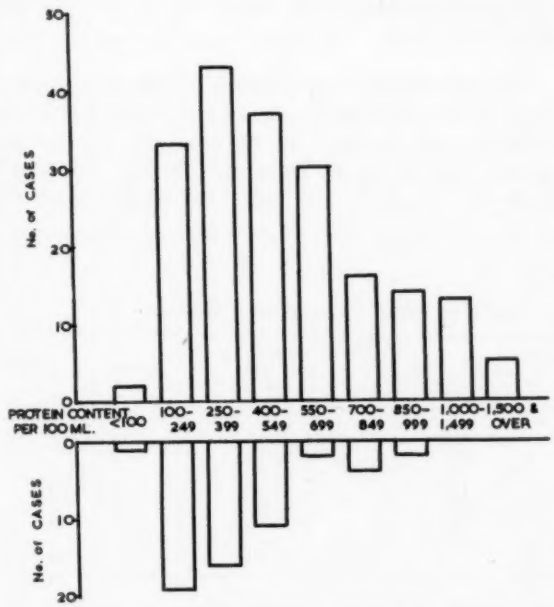

FIG. 6.—Histogram showing the distribution of cases according to the protein content of the C.S.F. 24 hours after P.P.D. As before, the natural conversions are shown above the line and the vaccinated below. By contrast with Fig. 4, the incidence declines quite smoothly without any sign of a second peak. The higher protein contents among the natural conversions as compared with the vaccinated is easily seen.

gap. These derive from 16 cases of disseminated sclerosis and 10 control cases made up of five cases of motoneurone disease, three of Huntington's chorea, and two of Parkinson's disease. From a simple comparison of the means of the cell counts 24 hours after injection in the two groups, they conclude that there is no significant difference between them. If, however, the distribution of the cell counts is considered (Fig. 5) the fallacy of this conclusion becomes obvious. Allowing for the difference in the total numbers, the distribution of their cases of disseminated sclerosis—all natural conversions—is remarkably like that in Fig. 4. All the cell counts but one were less than 600 per c.mm., that is to say, they belong to the "low-cell" group, while in the remaining one the cells were over 1,500 per c.mm., typical of the "high-cell" group.

Of the control group, in four the reaction, as judged by both the cells and the protein, was negligible, while in the remaining six the cell counts were all above 600 per c.mm. Even with so few cases in each group this difference in distribution is highly significant ($P = <0{\cdot}01$). More observations on the important question of specificity are badly needed; but such data as there are suggest that this distortion of the first phase of the reaction is not simply a function of chronic neurological disease as such.

The above data of Marshall and O'Grady were analysed by the use of the non-parametric Wald-Wolfewitz runs test. This test is sensitive to simple differences of any type whatever—central tendency, variance, skewness, or distribution. The scores from the independent samples are combined and ranked in order of magnitude, and the number of runs in the series determined. (A run is a sequence of scores from the same sample.) If the samples were identical in every way the scores would be distributed randomly, like well-shuffled cards. Difference in any parameter will produce aggregates of the two scores (clumping) and clumping will reduce the number of runs. The fewer the runs the less likely that the samples would be drawn from a common population. In this case a total of five runs was obtained and from the published table, and allowing for the small numbers, a total of seven runs or less will occur only once in 20 trials. Thus a total of five is significant at a level of better than 1%.

The Protein Content.—Comparison of the protein content of the C.S.F. of the first phase with the cell counts provides additional evidence that the "high-cell" cases form a distinct group within the series as a whole. Fig. 6 shows the distribution of cases according to the range into which the protein content falls. (As in Fig. 4, the natural conversions are shown above the line and the vaccinated below.)

By contrast with the cell counts, there is no sign of a second peak on the distribution curve for either group.

Comparison between the natural conversions and the vaccinated, however, shows that, though the shape of the distribution curve is much the same, the protein contents tend to be lower among the latter.

The peak incidence for the vaccinated lies to the left of that for the natural conversions and the percentages of cases in which the protein was less than 250 mg. per 100 ml. is twice as large among the natural conversions. At the other end of the scale, in no less than 78 of the natural conversions, *i.e.*, in 39·4%, the protein content reached 550 mg. per 100 ml. or more, as compared with eight, or only 14·6% of the vaccinated. This difference is significant at the 0·1% level ($\chi^2=11·53$, d.f.=1. $P<0·001$). Finally, in 17 of the "low-cell" cases, but only one of the "high-cell", 1 g. or more protein per 100 ml. was present.

Considering, then, Figs. 4 and 6 together, it is seen that, on the whole, the vaccinated tend to have higher cell counts and lower protein contents than the natural conversions, as well as having a much higher tolerance to P.P.D.

It is interesting to compare the protein contents for the cases in the several cell ranges since, if the height of the cell count is merely the expression of the intensity of the reaction, then the protein content should vary directly with the cell count.

Table VIII shows the range and mean value of the protein contents for the cases in each cell range for natural conversions, together with the number of cases in which the protein rose to 550 mg. per 100 ml. The natural conversions are separated from the vaccinated since their protein values are not comparable.

The Natural Conversions.—The 32 cases in which the cell counts are less than 100 per c.mm. are not strictly comparable with the rest, since they include those early cases which were admittedly under-treated. Among the rest, the mean protein is higher for those cases in which the cell counts were between 100 and 249, and which are also the most numerous. Thereafter, as the cell counts rise, so the mean protein content slowly declines, and the mean for the 18 "high-cell" cases is only 540 mg. per 100 ml. compared with 602 mg. per 100 ml. for the 58 cases with cell counts of between 100 and 249 per c.mm. This difference between the means is due to the scarcity among the "high-cell" group of cases in which the protein content rose to 550 mg. or more per 100 ml. As Table VIII shows, the proportion of cases with the high protein remains steady at about 46% of cases until the "high-cell" group is reached when it falls abruptly to 27·7%.

So far, then, from the protein contents rising with the cell count they appear to vary independently, and the "high cell" group of cases differs from the majority in that there is not the same tendency to produce the very high protein contents. In this respect too, then, as well as in the cell counts, these cases approximate more closely to the normal than do the rest.

The Vaccinated.—In Table VIII the protein contents in the vaccinated are set out according to the different cell ranges. In no case did the protein content rise to 1 g. or more per 100 ml. and in only eight did it reach 550 mg. As with the natural

TABLE VIII

RANGE AND MEAN VALUES FOR PROTEIN CONTENT IN EACH CELL COUNT RANGE

Cell Range	No. of Cases	Protein		Protein 550 g. and Over No.	Protein 1 g. or Over No.
		Range	Mean		
Natural Conversions					
<100	32	74-980	312	8 (22·6%)	—
100-249	55	109-1,790	602	26 (46·5%)	8 (13·8%)
250-399	40	180-1,860	580	18 (44·7%)	5 (13·1%)
400-549	24	134-1,240	538	11 (46·0%)	2 (8·3%)
550-999	24	110-1,225	529	11 (46·0%)	2 (8·3%)
1,000 and over	18	201-1,770	540	3 (27·7%)	1 (5·5%)
Total	193			76 (39·4%)	18 (9·3%)
Vaccinated					
<100	2	161-775	468	1	—
100-249	9	114-905	378	1 (11·1%)	—
250-399	17	70-804	354	2 (11·8%)	—
400-549	8	180-701	336	1 (12·5%)	—
550-999	8	127-946	284	1 (12·5%)	—
1,000 and over	11	250-617	403	2 (18·1%)	—
Total	55			8 (14·6%)	

conversions, among the "low-cell" cases the mean protein value declines as the cell counts rise from 378 mg. for those with cell counts of 100 to 249, to 284 mg. for those in the cell range of 550 to 999 per c.mm. For the "high-cell" group, however, the mean is rather higher, at 403 mg. per ml. Cell range for cell range, there is less difference between the vaccinated and natural conversion "high-cell" cases than between the "low-cell" groups. Indeed, excluding the solitary natural conversion in which both the cell count and the protein content exceeded 1,000, the mean protein value for the high-cell, natural conversions is 463 mg. per 100 ml., which is not much higher than the mean of 403 mg. for the vaccinated high-cell group.

Thus, among both the natural conversions and the vaccinated, the cell counts and protein contents vary independently so far as the low-cell cases are concerned. The high-cell cases among the vaccinated closely resemble the high-cell cases among natural conversions, and it is this minority group that, with regard to both the cell counts and protein contents, the first phase of the reaction approximates most closely to the normal.

Other Differences between High- and Low-cell Groups.—Granted, then, that in this series the cases can be divided into two groups according as to whether or not the first phase of the reaction develops normally, it remains to show whether these two groups differ in other respects. They have been compared for age, duration and pattern of disease, Mantoux status, and dosage without any outstanding difference, though the high-cell cases may possibly be rather the more tolerant of P.P.D. Our studies of the different protein fractions in the C.S.F. are not yet sufficiently advanced to show whether or not the behaviour of any fraction or fractions can be correlated with the development of the first phase. Simple quantitative estimation of the γ-globulin component of the resting C.S.F. has, however, shown no difference between the high- and low-cell cases, though confirming the finding that, in disseminated sclerosis, it is usually elevated.

So far, the only other differences found between the low- and high-cell cases are the sex distribution and the immediate prognosis.

TABLE IX

SEX DISTRIBUTION RELATED TO CELL COUNTS IN NATURAL CONVERSIONS

Cell Range	No. of Cases	No. of Males
<100	32	18 (56·25%)
100-249	55	29 (52·7%)
250-399	40	19 (47·5%)
400-549	24	9 (37·5%)
550-699	15	5 (33·3%)
700-999	9	2 (22·2%)
1,000 and over	18	10 (55·5%)
Total	193	92 (47·6%)

Sex Distribution in Relation to Cell Counts.—As has already been shown, the incidence of males among the vaccinated is unexpectedly low. In order,

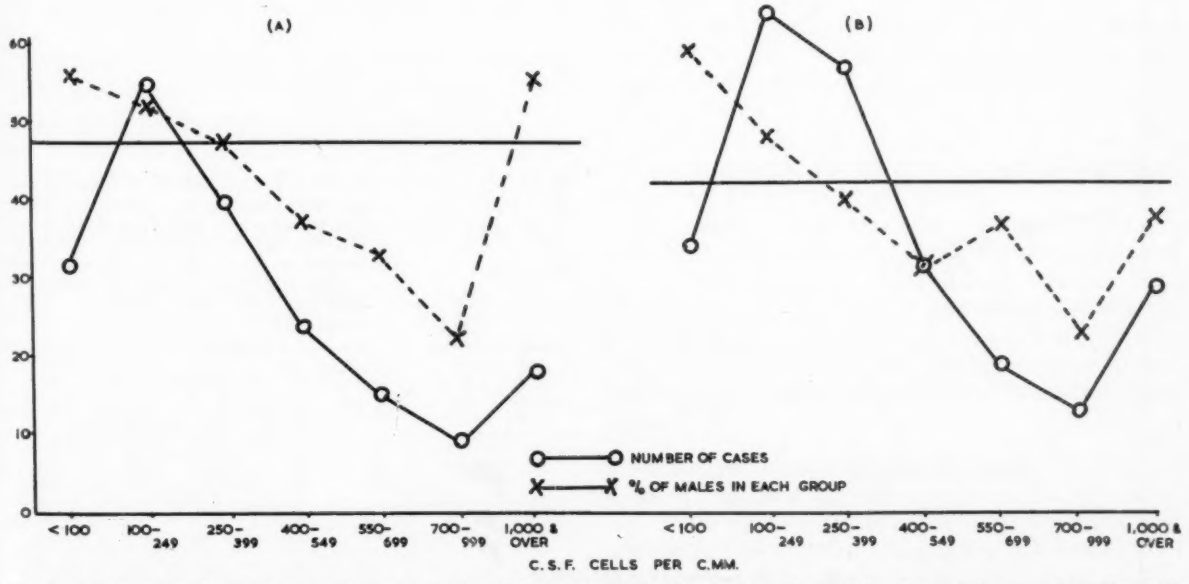

FIG. 7.—The number of cases in each cell range, together with the percentage of males in each group for the natural conversions (a) and the whole series (b). The horizontal lines show the expected percentage of males, *i.e.*, the percentage of males in the natural conversions as a whole and in the total series.

In (a) the percentage of males declines steadily as the cell counts rise until the high-cell group is reached when it rises sharply. In (b) the same relationship is preserved in spite of the inclusion of the vaccinated.

therefore, to avoid the possible introduction of a second and complicating factor, consideration of the relation between the sex distribution and the cell counts is, in the first instance, limited to the natural conversions. In Table IX these cases are set out according to the cell counts. For each cell range the total number of cases is shown, together with the number and percentage of males it includes. Throughout the low-cell cases the percentage of males falls steadily and significantly as the cell counts increase. When, however, the high-cell cases are reached this inverse relationship no longer holds: on the contrary, these cases again include a high percentage of males. This relationship, and the aberrant behaviour of the high-cell cases, is shown diagrammatically in Fig. 7(a) in which the total number of cases in each cell range, and the percentage of these cases that are males, are plotted beside one another. The horizontal line shows the expected percentage of males, that is to say, the percentage among the natural conversions as a whole.

In Fig. 7(b) the total number of cases and the percentage of males for each cell range are similarly set out, but for the series as a whole. It is clear that the inclusion of the vaccinated does not alter the shape and relationship of the curves, in spite of the paucity of males among them.

It appears, therefore, that among the low-cell cases there is a marked tendency for the men to produce the lower cell counts and the women the higher. This effect of sex is, however, not operative among the high-cell cases, where the percentage of males approximates to that for the series as a whole.

Sex Distribution in Relation to Protein Contents.—Table X shows the natural conversions set out according to the protein content. For simplicity's sake four protein ranges have been taken as measured in mg. per 100 ml.: less than 350, 350 to 549, 550 to 999, and 1,000 and over. The number of cases falling into each range is tabulated, together with the number and percentage of males it contains. Here, the percentage of males increases with the increase in protein content, a relationship which is clearly shown in Fig. 8(a), when the total number of cases and the percentage of males within each group are set out and where, as in Fig. 7, the horizontal line marks the expected percentage.

TABLE X

SEX DISTRIBUTION RELATED TO PROTEIN CONTENT IN NATURAL CONVERSIONS

Protein Range	No. of Cases	No. of Males
<350	60	25 (42·0%)
350-549	58	26 (45·0%)
550-999	55	28 (55·0%)
1,000 and over	20	13 (65·0%)
Total	193	92 (47·6%)

Fig. 8(b) shows the same quantities as Fig. 8(a),

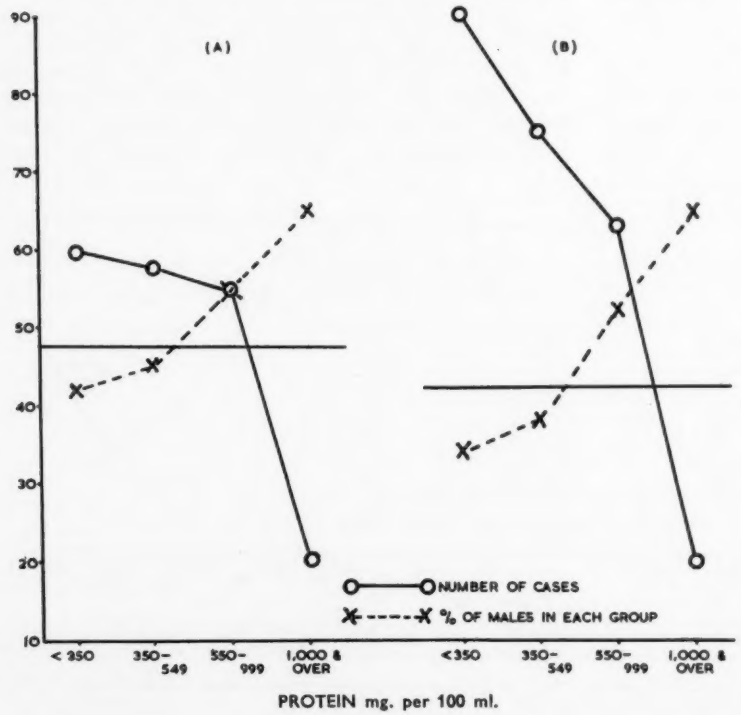

FIG. 8.—As in Fig. 7 but for the protein content; (a) natural conversions; (b) whole series. The percentage of men rises progressively with the rise in protein content. This is not affected by the inclusion of the vaccinated in spite of the increase in the number of cases with a low protein content.

but for the series as a whole. Here the inclusion of the vaccinated, with their tendency towards a low protein content, causes the curve for the total number of cases to decline more regularly. The sustained increase in the percentage of males with the increase in protein, and its sharp departure from the expected level, is even more obvious.

In summary then, among the low-cell cases the reaction in males tends to produce fewer cells and more protein than in females. This relationship, however, does not hold for the high-cell cases, which include a relatively large number of men in spite of the high-cell counts and comparatively low protein contents. In other words, in those cases in which the first phase of the reaction develops normally, it does so irrespective of sex: for the rest, the males show a greater departure from the normal than do the females.

Immediate Prognosis in Relation to Cell Counts.—By immediate prognosis is meant the course of the illness during the first year after treatment. Disregarding all remissions we have assessed this simply from the relapse rate. The criteria by which relapse is diagnosed are discussed in the clinical paper. For present purposes steady deterioration after treatment is equated with relapse. Of the 248 patients in the present series, 230 were followed for six months, and during this time 199, or 86·5%, did not relapse. Two hundred of them also completed a second six-month period of observation; of these 142, or 71%, were free from relapse throughout the year.

When, however, the cases are divided according to the cell counts, it is seen that the relapse rate is significantly higher among the high-cell cases than among the rest.

Table XI shows the cases set out according to the different ranges of cell counts. (Those in which the counts fall between 550 and 999 per c.mm. have been combined in order to make the numbers in the different groups more comparable.) Throughout the different ranges comprising the low-cell group as a whole the percentage of those free from relapse, either at the end of six months or at the end of the year, remains fairly constant. When, however, the high-cell group is reached there is a sharp drop: this is already apparent at the six months follow-up, and is obvious at the end of the year (Fig. 9).

TABLE XI

PROGNOSIS RELATED TO CELL COUNTS

Cell Range	No. Followed		No. without Relapse		% without Relapse	
	6 mth.	1 yr.	6 mth.	1 yr.	6 mth.	1 yr.
<100	31	31	29	24	94	77
100-249	60	55	52	40	87	73
250-399	56	47	48	34	85	72
400-549	29	23	26	15	90	70
550-999	27	26	24	22	89	86
Total <1,000	203	182	179	135	88	74
1,000 and over	27	18	20	7	74	39
Total	230	200	199	142	86·5	71

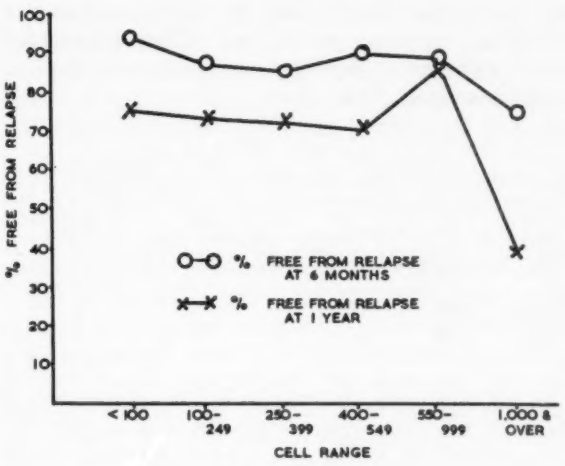

FIG. 9.—The percentage of cases without relapse, both at the end of six months and at the end of one year, is plotted against the cell range. The sharp decrease in cases without relapse among those in which cell counts of 1,000 or more were obtained is detectable at the end of six months and obvious at the end of one year.

Thus, of the 203 low-cell cases followed for six months, 88% survived without relapse compared with 74% of the 27 high-cell cases. At the end of one year 74% of the 182 low-cell cases have survived compared with only 39% of the 18 high-cell cases. In spite of the disparity between the total numbers in the two groups the difference at one year is significant ($\chi^2=8{\cdot}27$, d.f.$=1$; $0{\cdot}01>P>0{\cdot}001$).

In summary, then, the immediate prognosis has proved to be considerably worse for the high- than for the low-cell cases. This finding, together with the fact that, within the limits of the low-cell group as a whole, the immediate prognosis does not vary with the cell count, provides further support for the view that the high-cell cases differ qualitatively from the rest.

Immediate Prognosis in Relation to Protein Content.—During the course of this study evidence has accumulated suggesting that the freedom from relapse after treatment is related to the intensity of the reaction as gauged from the rise in the protein content. Comparison between the protein content 24 hours after the injection and the subsequent relapse rate, however, revealed no correlation

between the two except when the protein content rose to 550 mg. or more per 100 ml. Then the relapse rate at six months, and still more at one year, showed a significant fall (Table XII).

TABLE XII

PROGNOSIS RELATED TO PROTEIN CONTENT

Protein Range (mg./100 ml.)	No. Followed		No. without Relapse		% without Relapse	
	6 mth.	1 yr.	6 mth.	1 yr.	6 mth.	1 yr.
<550	153	132	127	87	83	66
550 and over	77	68	72	55	93·5	81

It was shown above that one of the ways in which the high-cell cases differ from the low is that the concomitant rise in the protein content tends to be smaller. In case this is the factor that determines the poor prognosis in this group the series has been broken down according to both the cell counts and the protein content (Table XIII). The number of high-cell cases in which the protein rose to 550 mg. or more is too small to allow of a definite conclusion on this point, but certainly there is no striking difference between those with a high protein content and those with a low. Among the low-cell cases, on the other hand, the difference is significant at one year ($\chi^2=5{\cdot}41$, d.f.$=1$; $0{\cdot}005>P>0{\cdot}01$).

In conclusion, then, it may be said that, from the results obtained in this series, the first phase of the reaction in disseminated sclerosis is abnormal in approximately 90% of cases in that the cell counts are much too low. Further, these cases differ quantitatively from the remainder in regard to the protein content during the first phase, the sex distribution, and the immediate prognosis.

The Protein Content throughout the Reaction

The other major anomaly of the reaction noted in our preliminary report was the surprisingly high protein content in conjunction with the low cell count. The bromide test has provided further evidence that in disseminated sclerosis the reaction does tend to elevate the protein content unduly.

In the normal, and at equilibrium, the bromide ratio varies between about 0·25 and 0·5; in other words, the serum contains from about two to three times as much bromide as does the C.S.F. When the permeability of the blood-C.S.F. barrier is increased, the ratio rises. Given accurate methods of estimation this has proved an extremely sensitive test, and indeed provides the best method of measuring the permeability of the blood-C.S.F. barrier at present available for clinical use (Hunter, Smith, and Taylor, 1954). When the efficiency of the barrier is impaired protein tends to pass from the blood to the C.S.F. By estimating, therefore, both the protein content of the C.S.F. and the bromide ratio a measure is gained of the degree of increased permeability required to bring about any given elevation of the protein.

During the intrathecal tuberculin reaction, even in patients in whom the meninges are otherwise normal, the bromide ratio rises steeply, often to the order of unity or beyond. An identical effect is found in tuberculous meningitis (Smith *et al.*, 1955): indeed there is now a considerable body of evidence to show that the changes in the C.S.F. in that disease are simply the expression of repeated, spontaneous, intrathecal tuberculin reactions (Taylor, Smith, and Vollum, 1955). It is in order to measure the increase in permeability of the barrier that, throughout this study, the bromide ratio has been estimated as a routine.

In the present series data on the bromide ratio are available for comparison with the protein contents in 242 cases. Whereas in previous sections study of the protein contents has been limited to the values found 24 hours after the injection of P.P.D., here it is the highest values for both protein content and bromide ratio found at any time during the reactions that are considered.

Fig. 10 shows the relationship found between the protein contents and the bromide ratio in these 242 cases, in 100 cases of tuberculous meningitis in which the estimations were made immediately after the patients' admission to hospital, and in eight intrathecal reactions in psychotic patients.

TABLE XIII

PROGNOSIS RELATED TO CELL COUNT AND PROTEIN CONTENT

		550 and Over			<550			Total		
		No.	″s	%	No.	″s	%	No.	″s	%
1,000 and over	6 mth.	7	6	86	20	14	70	27	20	74
	1 yr.	6	2	33	12	5	42	18	7	39
<1,000	6 mth.	70	66	94	133	113	85	203	179	88
	1 yr.	62	53	86	120	82	68·3	182	135	74
Total	6 mth.	77	72	93·5	153	127	83	230	199	86·5
	1 yr.	68	55	80·9	132	87	66	200	142	71

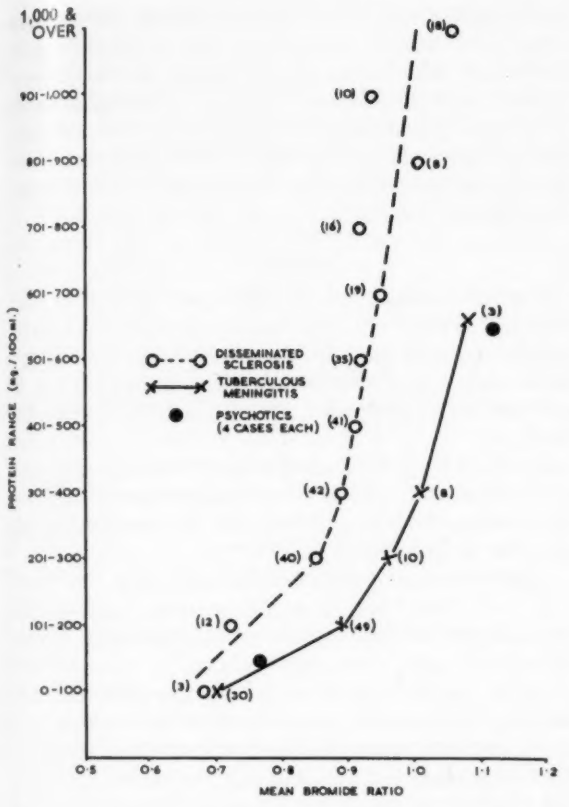

FIG. 10.—This illustrates the relation between the rise in protein content and in the bromide ratio during the intrathecal tuberculin reaction in both disseminated sclerosis and tuberculous meningitis.

Each protein range is plotted against the mean bromide ratio of the cases falling within that range. The figures in brackets show the number of cases from which the mean bromide ratio was calculated.

The curve for disseminated sclerosis lies to the left and above that for tuberculous meningitis, indicating that in that disease any given increase in the permeability of the blood-C.S.F. barrier, as measured by the bromide test, is accompanied by an excess of protein.

(For further explanation, and for evidence that the findings in tuberculous meningitis represent the normal, see text.)

The cases were divided according to the protein content into serial ranges of 100 mg. The mean value for the bromide ratios for the cases in each protein range was then calculated and plotted against the protein range. The cases of tuberculous meningitis were treated in the same way, except that as in only three cases did the protein content exceed 400 mg. per 100 ml.; for these three the means of both the protein contents and the bromide ratio were calculated and plotted against each other. Finally, of the eight psychotic cases, in four the maximal protein lay between 100 and 200 mg. per 100 ml., and in four between 400 and 600 mg. per 100 ml. The mean values for protein contents and bromide ratios in each set of four were calculated and plotted against each other.

It is at once apparent that the curve for disseminated sclerosis lies well to the left of that for tuberculous meningitis. In other words, the same increase in the bromide ratio is accompanied by a much greater increase in protein content in the former disease than in the latter. This difference is seen very clearly when the distribution of cases throughout the different protein ranges is studied. In spite of the uniformly higher bromide ratios among the cases of tuberculous meningitis, in only 3% did the protein content exceed 400 mg. per 100 ml., while in 79% it did not exceed 200 mg. per 100 ml. Among the cases of disseminated sclerosis, on the other hand, in 60% the protein content was more than 400 mg. per 100 ml., and in only just over 6% did it fail to exceed 200 mg. per 100 ml.

The question then arises as to which curve represents the normal. Here the findings in the cases of psychosis are important. Few as they are, it is obvious that they approximate closely to the curve for tuberculous meningitis, which strongly suggests that it is this one that exemplifies the normal. It is also interesting to note that in those cases of tuberculous meningitis treated with intrathecal P.P.D. in which the bromide ratio was estimated at the height of the reactions, the points for protein content and bromide ratio lie on the same curve as that for untreated tuberculous meningitis although rather higher up it.

If, then, the bromide ratio is accepted as a valid measure of permeability of the blood-C.S.F. barrier, and the evidence for this is good, then for any given increase in permeability the C.S.F. in disseminated sclerosis contains more than the expected amount of protein.

Discussion and Conclusions

The idea that hypersensitivity plays a part in the natural history of disseminated sclerosis is, of course, not new. The discovery that, under suitable circumstances, brain tissue could act as an antigen and provoke a reaction resulting in demyelination lent strong support to this idea, and numerous attempts have been made to incriminate allergy as a factor in pathogenesis (McAlpine *et al.*, 1955). But, so far as we know, these attempts have been exclusively concerned with the immediate or anaphylactic type of immune response, whereas the present study is solely concerned with delayed or tuberculin type sensitivity.

The observations recorded here on the intrathecal tuberculin reaction fully support our preliminary report that, in the great majority of cases of disseminated sclerosis, the pattern of the reaction is

consistently distorted. Moreover, attempts to produce Mantoux conversion in those patients who were tuberculin negative not only confirm the presence of an immunological abnormality in this disease, but show that it is not confined to the central nervous system but affects the body as a whole. The nature of the mechanism whereby the acquisition of skin sensitivity is interfered with, and the cellular component of the intrathecal reaction depressed, while the production of protein is enhanced, remains obscure though, from the sex differences described, it is presumably susceptible to hormonal influence.

The part, if any, which the immunological abnormality plays in the pathogenesis of the disease is almost equally obscure. The presence of a demonstrable immunological abnormality with systemic involvement, and the possible hormonal factor, even the classical relapsing-remitting course, at once suggest an auto-immune disease. On the other hand, it is probable that the abnormality in Mantoux conversion develops together with the disease, and there is also the curious finding that it may be associated with facilitation of remission. Somewhat in line with this is the, to us, unexpected finding that, after treatment, the immediate relapse rate has varied inversely with the abnormality of the reaction. In view of this, it is possible that the immunological anomalies, so far from reflecting the disease process as such, are the expression of some defence mechanism.

So far the question has been begged of whether the freedom from relapse in the "low-cell, high-protein" cases (Table XIII) is the result of treatment, or whether the pattern of the reaction has merely served to distinguish those cases in which the prognosis is naturally good. We incline to the former view. Certainly there was nothing in the course of the disease before treatment in these cases to suggest that so many patients were about to enter on a period of arrest; on the contrary, in many the disease was taking a progressive course. It is also worth noting that of those in whom the protein content failed to reach a high level, 33% relapsed during the subsequent year, a figure which agrees very well with the average annual relapse rate in many published series (*e.g.*, McAlpine *et al.*, 1955). We, therefore, postulate that in those cases in which a high protein content is achieved the chance of a relapse during the next year is lessened while for the remainder it is unaffected.

But whichever is the right interpretation, one thing is very clear: the demonstration that the relapse rate is related both to the cell count and to the protein content of the reaction has enormously increased the difficulty of planning a valid controlled therapeutic trial. On the one hand, only those among the treated group in whom a high protein level is reached can be reckoned as adequately treated; and on the other, factors of demonstrable prognostic significance are now so numerous that inconveniently large numbers will be required before it can be assumed that the controls and treated cases are properly matched.

Summary

Former studies on the place of allergy in the natural history of disseminated sclerosis have usually been limited to the immediate or anaphylactic type of hypersensitivity. The present study is confined to the delayed or tuberculin type of immune reaction.

Study of the intradermal and intrathecal response to tuberculin in 248 cases of disseminated sclerosis has confirmed our earlier finding of an immunological disorder in this disease.

Serial Mantoux tests have shown that, by contrast with the findings in tuberculosis and in the general population, men are significantly more sensitive to tuberculin than women.

B.C.G. or vole bacillus vaccination of Mantoux-negative patients has shown that the conversion rate is low and the reversion rate high, findings reminiscent of sarcoidosis. By contrast with that disease, the addition of small amounts of cortisone to the tuberculin has not affected the results of the test.

The intrathecal reaction was examined with special reference to (*a*) the first phase of the reaction, *i.e.*, to the C.S.F. changes 24 hours after the lumbar injection of P.P.D.; and (*b*) to the highest protein content in the C.S.F. at any time during the reaction.

The cellular component of the first phase of the reaction was found to be partially suppressed in approximately 90% of cases. Moreover, those in which it developed normally differed from the majority in regard to the protein content of the same specimen of C.S.F., in the distribution of the sexes, and in the immediate prognosis. It is therefore concluded that this series is not homogeneous but consists of a large majority group—called the "low-cell" group, and a small minority group, the "high-cell" group—that differ qualitatively from one another.

The vaccinated tend to have rather higher cell counts and considerably lower protein contents than do the natural conversions. The reaction thus approximates more closely to the normal. This does not seem to vary with the ease or difficulty of Mantoux conversion.

Within the low-cell group the distribution of the sexes is not uniform in that, as judged both by the cell counts and the protein contents, the greater the

departure from the normal, the higher the proportion of males.

Throughout the high-cell group the immediate prognosis is bad, as judged by the relapse rate during the first year after treatment. Among the low-cell cases the prognosis for those in which the protein content of the first phase reached 550 mg. per 100 ml. is significantly better than in the rest. Reasons are advanced for attributing this improved prognosis to the treatment.

It is pointed out that the demonstration that the immediate relapse rate varies both with the cell counts and the protein contents makes the planning of a valid controlled trial very difficult.

Comparison of the relationships between the maximal protein content and bromide ratio in disseminated sclerosis, tuberculous meningitis, and in different kinds of psychosis, shows that, for any given increase in the permeability of the blood-C.S.F. barrier as measured by the bromide test, the C.S.F. in disseminated sclerosis contains an excess of protein.

It is concluded that in disseminated sclerosis there is a disorder of the delayed type of hypersensitivity and that this is not limited to the central nervous system but affects the body as a whole. The possible bearing of these findings on pathogenesis is discussed, and it is pointed out that they are compatible with the hypothesis that disseminated sclerosis is an auto-immune disease. It is, however, possible that they reflect a defence mechanism rather than the disease process itself.

We wish to express our gratitude to Mr. Barr, of the Oxford Regional Hospital Board, for his help with the general statistical aspects of this work; to Dr. C. Ounsted for his analysis of the data of Marshall and O'Grady, and also to Dr. R. L. Vollum for the W.V.V. vaccinations. We also wish to thank the medical, nursing, and laboratory staffs of the United Oxford Hospitals, Stoke Mandeville Hospital, and the Military Hospital for Head Injuries, Wheatley, for their invaluable help. Finally, we are deeply indebted to the Trustees of the Nuffield Foundation whose generous support has made this work possible.

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THERAPEUTIC TRIALS IN MULTIPLE SCLEROSIS

PRELIMINARY REPORT ON EFFECTS OF INTRATHECAL INJECTION OF TUBERCULIN (P.P.D.)

BY

HENRY MILLER, D. J. NEWELL, ALAN RIDLEY, and KURT SCHAPIRA

From the Royal Victoria Infirmary and the Medical School, Newcastle upon Tyne

In 1957, Smith, Espir, Whitty, and Russell described what they regarded as characteristic changes in the spinal fluid of patients with multiple sclerosis following intrathecal injection of tuberculin (purified protein derivative, P.P.D.). They regarded these changes as indicating an abnormal and possibly specific immunological reaction, suggested that the administration of P.P.D. "might be beneficial in multiple sclerosis", and quoted initial clinical observations which seemed to lend some support to this view. The spinal fluid changes described were seen only in Mantoux-positive patients, and comprised an apparent suppression of the initial polymorphonuclear response seen in similar control (psychotic) patients similarly injected, with a subsequent exudation of mononuclear cells and a disproportionate biphasic rise in protein content. Marshall and O'Grady (1959) have subsequently demonstrated that spinal fluid changes similar to those encountered in multiple sclerotic cases are also seen after the intrathecal injection of P.P.D. in Mantoux-positive patients with other chronic neurological disorders such as motor neurone disease and Parkinsonism, an observation which they interpret as indicating the non-specific nature of the response without in any way "nullifying the suggestion that this treatment may be of benefit".

Although the reason for endowing this procedure with any possible therapeutic significance has never been clearly stated, we felt it important that the suggestion should be subjected to carefully controlled assessment, and it is with the preliminary results of such a trial that the present paper is concerned.

Material

The trial, which is still in progress, is to include 90 moderately disabled patients randomly allocated amongst three treatment groups whose management is conducted under similar conditions. One group is given intrathecal P.P.D., one intrathecal saline, and one is subjected to simple spinal punctures. During the treatment period each patient received in addition a three-week standardized course of physiotherapy.

Up to the present, 82 patients have been included in the trial, and the original intention was to defer assessment of results until two years after the treatment of the ninetieth patient had been completed. Our decision to report here the results of a preliminary analysis of 44 patients in whom more than 12 months have elapsed since the completion of treatment has been dictated by the considerable pressure to which neurologists in various parts of the United Kingdom have been subjected by patients who are anxious for them to undertake this form of treatment on the basis of present evidence.

In addition to the 44 cases in the trial proper, the present interim study includes 13 further patients with chronic multiple sclerosis to whom we had administered P.P.D. before the trial began. Because of death or unwillingness to participate further, four "trial" patients and three "pre-trial" patients could not be reviewed, and analysis is therefore based on the remaining 40 "trial" and 10 "pre-trial" patients. Of the 40 trial patients, 14 had lumbar puncture only, 12 received intrathecal saline, and 14 were given intrathecal P.P.D. The status of the patients before treatment was instituted is summarized in Table I.

The lumbar puncture (LP) group contained six men and eight women, the saline (S) group eight men and four women, and the P.P.D. group seven men and seven women. The pre-trial P.P.D. patients comprised six men and four women.

The mean age of onset of the disease was 33·5 years (LP), 31·3 years (S), 32·4 years (P.P.D.), and 26·3 years (pre-trial P.P.D.). At the onset of treatment the mean duration of the disease was 10·4, 8·0, 7·0, and 9·7 years respectively.

With regard to the course of the disease up to the time of the trial, the LP group comprised 11 patients in whom the disease had progressed slowly and three in whom the course showed exacerbations and remissions; the S group comprised one rapidly progressive, eight slowly progressive, and three exacerbating and remitting cases. In the P.P.D. group there were one rapidly progressive, 10 slowly progressive, and three exacerbation-remission cases; whilst among the pre-trial P.P.D. cases there were seven in whom the disease was of slow progression and three in whom its course had exhibited exacerbations and remissions.

The functional grade of patients was also recorded initially and at each subsequent examination. The

grades employed were grade I, symptom free; grade II, symptoms but unrestricted activities; grade III, moderately restricted; grade IV, markedly restricted; grade V, confined to home; grade VI, immobile at home; grade VII, bedridden. At review, specific enquiry was made about any acute exacerbations experienced, and the patients were also asked if they thought their condition had improved, deteriorated, or remained unchanged.

The Alexander scoring system (Alexander, Berkeley, and Alexander, 1958) was used to record the results of clinical examinations carried out before treatment and at the time of re-assessment.

Eight patients had received previous medication. This consisted of vitamin B_{12}, liver injections, or arsenical therapy, and this group included one patient in the LP group, four in the S group, one P.P.D. case, and two pre-trial P.P.D. patients. No patient was included in the trial who had received any such treatment during the preceding year.

The random allocation had thus produced three trial groups comparable in all the relevant respects mentioned.

Method

P.P.D. and Pre-trial P.P.D. Patients.—Before beginning intrathecal injections the following preliminary investigations were carried out: (1) Chest radiograph; (2) serial Mantoux testing, using dilutions of 1 : 10,000, 1 : 1,000, 1 : 100 (since only Mantoux-positive patients will show the described response to intrathecal tuberculin, any Mantoux-negative patients were first "converted" with B.C.G.); (3) E.S.R., full blood count, and blood urea estimations; (4) microscopic examination of urine to exclude infection.

The tuberculin (P.P.D.) obtained from the Ministry of Agriculture and Fisheries Veterinary Laboratory at Weybridge was made up into "standard" P.P.D. (Smith *et al.*, 1957) which contains 7·5 μg. of P.P.D. per ml.

At lumbar puncture a specimen of spinal fluid is collected for cell count and protein estimation, and 0·5 ml. of 1 in 10 standard P.P.D. introduced into the lumbar sac. Temperature and pulse are recorded four-hourly. Twenty-four hours after the administration of the P.P.D., spinal fluid is collected to determine whether cells and protein have risen. A "satisfactory reaction" is considered to have taken place if the rise in spinal fluid protein exceeds 100 mg. per 100 ml. If the protein rise is less than this figure, a further lumbar puncture is carried out three days later, and if the increase in the protein level of the fluid has still not exceeded 100 mg. % the response is recorded as "no reaction". Should there have been no reaction, 1·0 ml. of 1 in 10 standard P.P.D. is given, and if this dose fails to produce a reaction, 1·5 ml. of 1 in 10 standard P.P.D. solution is injected.

When a reaction has occurred, no more P.P.D. is given until the spinal fluid protein content has fallen to below 100 mg. %. Two reactions constituted a "course" of P.P.D. In the pre-trial P.P.D. group, three reactions were induced in two patients. All the reactions in both P.P.D. and pre-trial P.P.D. groups fulfilled the above criteria, and the mean increases in the spinal fluid protein induced by both first and second injections of P.P.D. were 260 mg. % (P.P.D. group) and 290 mg. % (pre-trial P.P.D. group).

The "P.P.D. reaction" was usually accompanied by a constitutional illness with some degree of meningism, and occasional more alarming complications included severe clinical meningitis with troublesome vomiting (four cases), retention of urine (four, including one requiring three weeks' catheterization), coma (two), dysphagia and dysarthria. In three further patients severe exacerbations of the chronic disease caused some alarm during treatment, and in one of these instances a profound difficulty in walking did not fully recover.

Saline Group.—These patients received two intrathecal injections of 0·5 ml. and 1·0 ml. of normal saline separated by an interval of seven to 10 days; and each injection was followed 24 hours later by lumbar puncture for estimation of cell and protein content of the spinal fluid. The changes observed were trivial and evanescent.

Lumbar Puncture Group.—Patients in this group had one lumbar puncture followed by a further puncture seven to 10 days later.

Assessment

Disability was assessed and scored by an observer who was unaware of the patient's treatment group

TABLE I

COMPA RISON OF GROUPS BEFORE TREATMENT

	Trial Treatment			Pre-trial Group P.P.D.
	Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.	
Number in Group	14	12	14	10
Males	6	8	7	6
Females	8	4	7	4
Mean age at onset of multiple sclerosis	33·5 yr.	31·3 yr.	32·4 yr.	26·3 yr.
Mean age at start of treatment	43·9 yr.	39·3 yr.	39·4 yr.	36·0 yr.
Course of disease: Rapidly progressive	—	1	1	—
Course of disease: Slowly progressive	11	8	10	7
Course of disease: Exacerbation-remission	3	3	3	3
Functional grading: III	10	8	10	7
Functional grading: IV	4	4	4	1
Functional grading: V	—	—	—	—
Functional grading: VI	—	—	—	2
Alexander classification (mean)	200·3	219·0	201·6	241·0

TABLE II

COMPARISON OF THE GROUPS AFTER TREATMENT

	Trial Treatment			Pre-trial Group P.P.D.
	Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.	
Period between treatment and assessment (mean)	14 mth.	16 mth.	15 mth.	33 mth.
Functional grading III	9	5	9	3
Functional grading IV	3	7	4	2
Functional grading V	1	—	1	1
Functional grading VI	1	—	—	3
Functional grading VII	—	—	—	1
Deterioration score	+27·6	+34·2	+33·4	+74·2
Number of acute exacerbations since treatment	1	1	6	1
Patients' assessment after treatment Improved	5	3	3	1
Patients' assessment after treatment Same	4	3	5	2
Patients' assessment after treatment Worse	5	6	6	7

at the time of his examination. Seven patients were not available for this initial review. Of these, three declined to be re-examined, one could not be traced, and three had died. One male patient died suddenly after an attack of bronchopneumonia 18 months after receiving intrathecal saline, and the other two deaths occurred in pre-trial P.P.D. patients, three and 13 months respectively after receiving this form of treatment. In each instance death occurred in toxaemia associated with intractable chronic urinary infection which originated during catheterization necessitated by treatment.

Results

These are summarized in Table II.

Acute Exacerbations.—Discounting the immediate neurological exacerbation which often accompanied a "reaction" in patients injected with P.P.D., six patients in the three trial groups experienced eight subsequent exacerbations during the period of observation following treatment, which has so far covered a total of 580 patient-months. This indicates that one acute exacerbation occurred during every 73 patient-months: in a trial of maintenance treatment with prednisolone, salicylate, and dummy tablets recently concluded (Miller, Newell, and Ridley, 1961) the comparable figure during 18 months' observation in 79 patients who had suffered from the disease for an average period of about 12 years was 75 patient-months per exacerbation. Four of the patients who relapsed had received P.P.D., and one exacerbation occurred in each of the other groups. One of the P.P.D. cases had three exacerbations. These figures are too small to be statistically significant.

Alexander Scores.—A positive change in the Alexander score indicates clinical deterioration. All three of the trial group scored an average of about +30 points on the Alexander scale, and the changes in score did not differ significantly between the three treatments.

The pre-trial P.P.D. patients, with an average deterioration score of +74·2 points, were significantly different from the trial patients ($t=2{\cdot}27$, $P<0{\cdot}05$). This result is consistent: after twice as long these patients had deteriorated twice as much.

Functional Grading and Patients' Subjective Assessments.—In neither instance did comparison in these respects reveal any significant difference between the three trial groups.

Conclusions

These observations have failed to reveal any influence of the injection of intrathecal tuberculin on the subsequent clinical course of multiple sclerosis by comparison with that of saline injection or simple spinal puncture. In more than half the patients treated, the injection of tuberculin provoked an immediate clinical exacerbation of the chronic disease, with the reactivation of old symptoms and the provocation of new, but the present observations lend no support to the contention that the procedure influences the subsequent progression of the disease for good or ill once the immediate effects of treatment have subsided. It is possible that further observations may lead us to revise this assessment, but in the meantime it seems hardly justifiable to regard the intrathecal administration of tuberculin as a form of treatment for this disease.

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GAMMA GLOBULIN STUDIES IN MULTIPLE SCLEROSIS AND THEIR APPLICATION TO THE PROBLEM OF DIAGNOSIS

BY

KURT SCHAPIRA and DOROTHY C. PARK*

From the Department of Neurology and Section of Chemical Pathology, Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne

The demonstration of the association between a positive colloidal gold reaction and an increase in the γ-globulin in the cerebrospinal fluid (Kabat, Landow, and Moore, 1942) has stimulated further study of this protein fraction. An increase in this moiety in the spinal fluid of patients with multiple sclerosis has been reported by workers using free-solution and paper electrophoresis, as well as immunochemical methods. It has been shown (Yahr, Goldensohn, and Kabat, 1954) that the serum γ-globulin remains unaltered, although changes have been reported in the serum albumin and α- and β-globulin concentrations (Volk, Saifer, and Rabiner, 1954; Press, 1956). The present study is primarily concerned with the γ-globulin fraction of the cerebrospinal fluid as determined by filter paper electrophoresis. The application and limitations of this estimation in the diagnosis of multiple sclerosis are discussed.

Material

The cerebrospinal fluids of 156 patients together with the sera in some of these cases were examined by means of paper electrophoresis. This series of patients consisted of three groups:—

Group 1: 81 Patients with Multiple Sclerosis.—In 13 patients the spinal fluid was examined during the first episode of the disease, and in 12 patients during an acute exacerbation characterized by significant worsening of existing symptoms or clinical evidence of fresh lesions of less than two weeks' duration. In the remaining 56 patients the disease was considered to be chronic: there were permanent symptoms (often with severe disability) which were slowly progressive or in some cases static. The diagnosis in all instances was unequivocal; doubtful cases were excluded from the study.

Group II: 50 Patients with Other Neurological Disorders.—These are listed in Table I.

Group III: 25 Control Cases.—These were regarded as "normal" for the purpose of this study, and consisted largely of patients with psychiatric illnesses, in whom clinical examination failed to reveal any evidence of organic nervous disease, and in whom spinal fluid examination by routine methods (protein, cells, Lange colloidal gold curve) gave results within the normal range. The clinical diagnoses in this group were depression (12 cases), hysteria (three), headache without abnormal physical signs and negative ancillary findings (three), anxiety state (two), and single cases of cough syncope, schizophrenia, otosclerosis, frontal sinusitis, and cerebral arteriosclerosis.

Method

Gamma globulin concentrations in cerebrospinal fluid and sera were estimated by quantitative filter paper electrophoresis. The procedure evolved in this study was designed for the analysis of small amounts of cerebrospinal fluid. In most cases about 5 ml. of spinal fluid was required, the precise volume depending upon the initial total protein concentration.

The total protein content was estimated by the method of Lowry, Rosebrough, Farr, and Randall (1951) which is a simple but sensitive colorimetric technique requiring only 0·1 or 0·2 ml. of spinal fluid. The cerebrospinal fluid was then concentrated to a protein content suitable for electrophoresis. This was achieved by means of ultrafiltration against negative pressure through Visking dialysis tubing. A convenient and reliable means of concentration is a most important feature of the analysis. Ultrafiltration was allowed to proceed until a protein concentration of approximately 2 g. per 100 ml. was obtained. The protein content of the sera was adjusted to similar concentration by dilution with saline.

Electrophoresis was carried out in the apparatus designed by Latner (1952) using Whatman No. 100 filter paper strips (46 cm. × 2 cm.) and barbitone buffer,

*Present address: Department of Pathology, University of Leeds.

TABLE I

DIAGNOSTIC ANALYSIS OF "OTHER NEUROLOGICAL CONDITIONS" WITH γ GLOBULIN VALUES

Condition	No. of Cases	Spinal Fluid γ Globulin as % of Total Protein
Epilepsy	10	13·3, 12·0, 11·6, 10·8, 10·5, 9·8, 7·8, 6·5, 5·8 4·6
Cerebral arterial diseases	7	19·0, 16·4, 15·4, 13·4, 11·6, 8·2, 4·7
Hereditary degenerative disorders	7	19·5, 18·5, 15·2, 14·0, 8·6, 7·7, 7·5
Cervical spondylosis	5	20·4, 14·4, 12·6, 12·4, 10·8
Migraine	3	13·7, 11·3, 10·0
Prolapsed intervertebral disc	2	12·3, 8·6
Motor neurone disease	2	12·7, 12·5
Spinal cord tumours	2	14·7, 12·0
Neurosyphilis	2	20·0, 15·8
Polyneuritis	2	25·5, 11·5
Brain tumour (metastases)	1	19·7
Muscular dystrophy	1	14·0
Subacute combined degeneration	1	11·0
Myalgia paraesthetica and Paget's disease	1	18·6
Polymyositis	1	17·5
Ménière's syndrome	1	7·4

TABLE II

MEAN VALUES AND STANDARD DEVIATIONS FOR γ GLOBULIN, ALBUMIN, A/G RATIO, AND TOTAL PROTEIN IN SPINAL FLUID

	No. of Cases	γ Globulin (as % of total protein)		Albumin (absolute amount) (mg./100 ml.)		Albumin: γ Globulin Ratio		Total Protein (mg./100 ml.)	
		Mean %	S.D.	Mean %	S.D.	Mean %	S.D.	Mean %	S.D.
Controls	25	11·1	±3·18	31·5	±9·32	6·6	±2·32	46·2	±12·36
Multiple sclerosis	81	22·4	±9·47	35·6	±9·74	3·5	±1·98	56·4	±13·42
Other neurological conditions	50	13·0	±4·57	38·0	±13·89	6·4	±3·20	58·6	±31·79

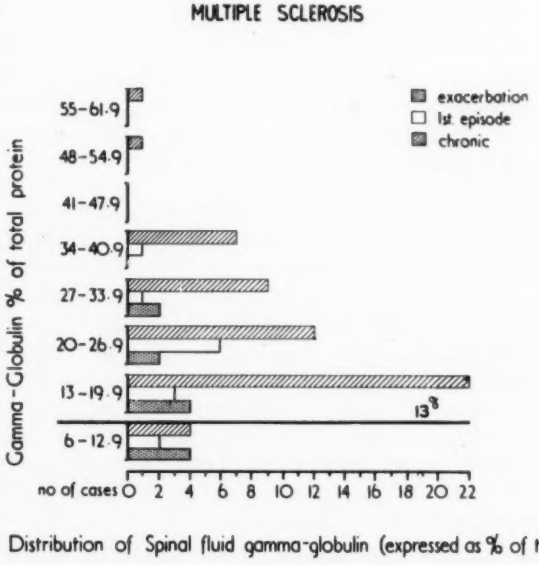
*p*H 8·6, μ0·05. A current of 0·4 mA per paper strip was applied for 16 hours. The strips were dried in a hot air oven and stained with Lissamine green. A double-beam automatic recording reflectance densitometer (Joyce, Loebel & Co., Ltd., Newcastle upon Tyne) was used to scan the stained strips. The method (Park, 1959) of analysing the diagrams obtained and the precautions taken will be published in detail elsewhere (Latner and Park, in preparation). Proof of the validity and reliability of the method was obtained by analysing protein mixtures containing albumin, β-, and γ-globulin in known proportions.

Results

The mean values and standard deviations of the albumin and γ-globulin fractions in the cerebrospinal fluid are given in Table II. This shows a highly significant increase of the γ-globulin fraction in multiple sclerosis when compared with the control group ($P<0.001$). There is also a highly significant increase of γ-globulin in multiple sclerosis when compared with the group of other neurological conditions ($P \ll 0.001$).

That this is due to an absolute increase in γ-globulin is demonstrated by the fact that the albumin/γ-globulin ratios show similar significant differences, whereas there is no significant difference when these groups are compared with respect to their absolute albumin content.

Applying a 99% upper confidence limit to the mean of the control group gives a value of 13% for the spinal fluid γ-globulin (expressed as a percentage of the total protein). Figure 1 shows that this value is exceeded in 88% of patients with multiple sclerosis; in 83% of patients in the first episode, in 67% of



Distribution of Spinal fluid gamma-globulin (expressed as % of t.p.)

FIG. 1

TABLE III

MEAN VALUES AND STANDARD DEVIATIONS FOR γ GLOBULIN, ALBUMIN, A/G RATIO, AND TOTAL PROTEIN IN SERUM

	No. of Cases	γ Globulin (as % of total protein)		Albumin (absolute amount) (g./100 ml.)		Albumin: γ Globulin Ratio		Total Protein (g./100 ml.)	
		Mean %	S.D.	Mean %	S.D.	Mean %	S.D.	Mean %	S.D.
Controls	16	21·5	±6·01	4·5	±0·64	3·1	±1·06	7·4	±0·80
Multiple sclerosis	27	20·6	±4·06	4·2	±0·66	3·1	±1·02	7·1	±0·61
Other neurological conditions	22	18·6	±4·29	4·8	±0·66	4·3	±2·27	7·6	±0·76

patients during exacerbations, and in 93% of chronic established cases.

Table III gives the mean values and standard deviations of the albumin and γ-globulin fractions in the sera examined. It is seen that the mean γ-globulin concentration in the multiple sclerosis group shows no significant difference from the control cases ($P > 0{\cdot}5$), or from the group of other neurological conditions ($P > 0{\cdot}6$).

In both Tables II and III we have expressed the γ-globulin fraction as a percentage of the total protein, since this value is then independent of changes in the total protein.

Discussion

In applying these results to the problem of diagnosis in multiple sclerosis, three aspects require particular consideration.

Does this method provide a greater aid in diagnosis than the usual routine laboratory examination of the spinal fluid? Secondly, in what percentage of multiple sclerosis cases is the γ-globulin content of the spinal fluid raised, both in the cases as a whole, and in various phases of the disease? This latter distinction we consider important, since an aid in diagnosis would be particularly valuable during the initial episode of the disease. Thirdly, and perhaps most important of all, does the estimation of γ-globulin help in the differentiation of multiple sclerosis from other neurological conditions with which it is likely to be confused clinically?

Figure 1 shows that a raised spinal fluid γ-globulin (>13% of total protein) was found in 88% of all cases of multiple sclerosis; conventional laboratory examination, however, revealed abnormalities in only 38% of these cases. It is apparent, therefore, that although the spinal fluid γ-globulin is not raised in every instance of multiple sclerosis, the high proportion of abnormal results yielded by this estimation is of clinical value. The pathogenetic significance of this finding is still far from clear and the assumption that it is a manifestation of an immunological disturbance has recently been questioned (Field and Ridley, 1960).

The γ-globulin levels in the various phases of the disease are graphically represented in Figure 1: an increase occurs in 93% of chronic established cases, in 83% of patients in the first episode, and in 67% of patients during exacerbations. The highest incidence of a raised γ-globulin level occurs in the spinal fluid of patients in whom the disease is well established, due to multiple lesions, and usually associated with marked disability, a finding which is in agreement with that of other workers (Yahr *et al.*, 1954). Although the clinical diagnosis usually presents little difficulty in this group of patients, we have included in our series five patients presenting with a featureless chronic paraplegia. Such cases are often presumptively regarded as instances of multiple sclerosis when myelography and other special investigations have failed to provide an alternative diagnosis. It has been our experience that routine spinal fluid examination has rarely furnished information of diagnostic value in this connexion, and it is of some interest, therefore, that the spinal fluid γ-globulin was raised in three of these five patients.

During the initial episode of the disease when diagnosis is important and often difficult, the γ-globulin level was raised in 10 out of 12 patients, whereas routine spinal fluid examination revealed abnormalities in only half of these cases.

A further analysis of conditions likely to be confused clinically with multiple sclerosis is of interest. Thus, the γ-globulin content was within normal limits in three out of five cases of cervical spondylosis, in both cases of prolapsed intervertebral disc, in three out of seven cases of hereditary degenerative disorders. Although the above constitute only a small number of cases, the diagnostic help which may be obtained from the estimation of gamma globulin is well illustrated in the following case:—

Mrs. D. B., a 27-year-old housewife, was first admitted under the care of Dr. Henry Miller in October, 1959, with a history of progressive weakness of both legs associated with some unsteadiness of 16 months' duration. The symptoms began quite abruptly while the patient was at a dance, and were followed soon after by some weakness

and clumsiness of both hands. There was no fluctuation of the severity of the complaints apart from the fact that the patient felt that her symptoms were less marked towards the end of the day.

The only other complaints were those of burning pains between her shoulder blades radiating down the spine, which followed a fall six months previously, and an occasional sensation of "pins and needles" in both calves.

Direct questioning revealed no other significant neurological symptoms, and her general health had been good apart from some weight loss (8 lb. in three months).

Her past history and family history revealed no significant features.

There were no abnormal physical signs in the cranial nerves. The arms were slightly spastic, but there was no wasting of the hands or fasciculation of muscles. Increased tone was very evident in both legs, and these features were associated with some weakness, marked increase of tendon reflexes, bilateral ankle clonus, and extensor plantar responses. There was no sensory loss, but some incoordination of both arms (R > L) could be demonstrated. The abdominal reflexes were retained. Full blood investigations, including Wassermann reaction and radiological studies of the skull, chest, and cervical spine, were normal. On lumbar puncture the pressure was 55 mm. of spinal fluid with normal manometrics. A clear colourless fluid was obtained with less than 1 cell per c.mm.; W.R. negative, Lange: 0000000000. The γ globulin content of spinal fluid was 3·8 mg. %, *i.e.*, 7% of total protein.

In spite of some unusual features, *i.e.*, retained abdominal reflexes and the absence of any sensory loss, a diagnosis of multiple sclerosis was considered to be the most likely. The low spinal fluid γ globulin content, however, was very much against this diagnosis, particularly since by this time symptoms were well established and the disease was progressing relentlessly.

The patient was seen at regular intervals in the outpatient department when in October, 1960, the correct diagnosis of motor neurone disease became obvious by the development of fasciculation of the tongue, and gross wasting of both arms. The patient had recently complained of marked difficulty in speaking and swallowing.

That an elevated γ-globulin content of the cerebrospinal fluid is not pathognomonic of multiple sclerosis and occurs also in some cases of a heterogeneous group of neurological disorders is illustrated in Fig. 2. A statistical comparison of the two groups, however, shows a highly significant difference ($P \ll 0.001$). It may also be seen from Fig. 2 that a figure of over 18% γ-globulin (expressed as % of total protein) is very suggestive of multiple sclerosis; no fewer than 62% of cases of multiple sclerosis gave figures above that level, compared with only 16% of the other neurological conditions, and 4% of the controls.

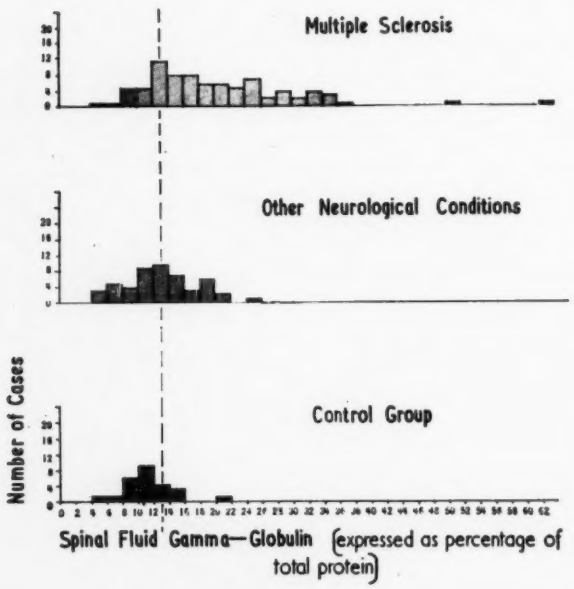


FIG. 2

Summary

Gamma-globulin levels in cerebrospinal fluid and serum have been estimated by means of quantitative paper electrophoresis.

Examination of the serum revealed no significant changes of this fraction in patients with multiple sclerosis.

However, a significant increase of γ-globulin was found in the cerebrospinal fluid of patients with multiple sclerosis when compared with the control group, this method yielding a much higher proportion of abnormal results than conventional laboratory examination.

The spinal fluid γ-globulin levels found in multiple sclerosis were also significantly higher than those found in a group of miscellaneous neurological disorders.

The estimation of γ-globulin in the cerebrospinal fluid is considered to be of help in the clinical diagnosis of multiple sclerosis.

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THE STIFFNESS OF SPASTIC MUSCLE*

BY

JOHN FOLEY

From the Centre for Spastic Children, Chelsea

This study stemmed from an attempt to find out whether simple physical manoeuvres have any measurable effect on the spastic state as such in small children with diplegia. Muscle tone is difficult to define except in crude clinical terms, but for the purposes of the present paper it can be defined simply as that resistance which is felt by the examiner's hand on passively extending a muscle. It was recognized clearly by early workers with the electromyogram (Weddell, Feinstein, and Pattle, 1944) that in both normal muscle at rest and in spastic muscle at rest there is no electrical activity, though in the case of the latter during stretching the electrical response is excessive, hypersynchronous, and subject to widespread irradiation. Hoefer and Putnam (1940), Lindsley, Schreiner, and Magoun (1949) and later Hoefer (1952) confirmed this, and indeed much of this early work served merely to demonstrate that the electromyogram alone can contribute little to our knowledge of states of muscular hypertonus. Combined with differential procaine block of the gamma efferents the technique has proved more rewarding (Rushworth, 1960). Weddell *et al.* (1944), however, made it clear that muscle tone is not merely a matter of the stretch reflex but must in part be due to the viscous and elastic properties of the muscles and tendons. A ballistic method for the measurement of the elastic property of skeletal muscle *in situ* in man was developed by Simonson, Snowden, Keys, and Brozek (1949) but has not proved of clinical value. There has been a tendency to regard "muscle tone" and "postural tone" as synonymous, but this is confusing, as there is tone in a normally innervated muscle which is not maintaining posture. Postural tone is a state of activity required to maintain a posture against gravity and is found, for example, in the long cervical muscles or the temporalis muscle as rhythmic motor unit activity with a frequency of 7 to 10 a second, instantly abolished by bringing the antagonists into action; while in the muscles of the back and legs it is found as occasional injections of activity into agonist and antagonist alternately to restore the body to a state of balance which is principally maintained by bones, tendons, and ligaments. Except in paraplegia in flexion the resting muscle of a spastic limb, if supported, is electrically silent, and yet its tone is high in comparison with normal or denervated muscle and becomes immediately higher on stretching. The purely mechanical component of muscle tone is present at rest and in movement, and both hypotonus and hypertonus are associated with a quantitative alteration in the physical property of the muscle. The neurogenic component of muscle tone is absent at rest, and is a complex state of hyperreactivity of the phasic and tonic stretch reflexes; and what determines the nature of the hypertonus appears to be the behaviour of the tonic part of the stretch reflex, and the timing of the lengthening reaction once stretching has begun. From the neurological point of view the spastic state comprises a number of phenomena which can be listed as follows: (*a*) low threshold of the stretch reflex, (*b*) increased reflexogenic area, (*c*) augmentation of the response, (*d*) irradiation of the response, (*e*) hypersynchrony of motor unit discharges, (*f*) desynchronization of the lengthening reaction, (*g*) contraction in agonist and antagonist, and finally (*h*) a particular distribution in the antigravity muscles. Not all of these are susceptible to measurement. Measurement of the threshold is too difficult for clinical purposes. The strength of a tendon jerk can be measured, provided the stimulus is of constant force; the technique of Buller and Dornhorst (1957) can be used with adult subjects but is too difficult to apply to young children. Hypersynchrony of motor units cannot be measured. The irradiation of the response to stretch can be mapped out but not measured. The response to relatively slow stretch, *i.e.*, of a speed not sufficient to elicit a tendon jerk is, however, more measurable. But the intact muscle spindle system is so designed that it will adjust itself continuously to increase in length or

*The material of this paper formed part of an essay which was awarded a prize by the South West Metropolitan Regional Hospital Board in 1958.

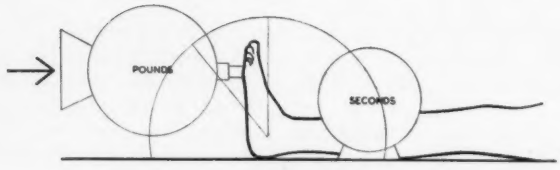

FIG. 1

tension of the muscle. The activity of such a system can only be measured by pitting against it another servocontrolled system which will provide either constant force throughout the movement, while the velocity is recorded, or constant velocity throughout a movement irrespective of resistance, in which case the force required is measured. Servocontrolled myotonometers have been constructed by Spiegel Wycis, Baird, Rovner, and Thur (1956), but the apparatus is costly, involves fixation of the limb and the cooperation of the subject, and is quite inapplicable to children. But the normal adult nervous system is of course servocontrolled and it can maintain a constant posture, or provide constant velocity against a changing resistance with surprising accuracy; and this fact, which is merely an expression of manual skill, is the basis of the method devised by Tardieu and his co-workers (Tardieu, Rondot, Mensch, Dalloz, Monfraix, and Tabary, 1957; Rondot, Dalloz, and Tardieu, 1958) for use with children, and of the simpler and more limited method described in this paper. Tardieu applied his method to the manual extension of the biceps at constant velocity, the force being measured by means of a strain-gauge through which is fed an A.C. signal, while the angular velocity of the elbow joint is recorded by a potentiometer giving a D.C. signal. He demonstrated that above a certain critical velocity of extension, which is the hallmark of spasticity, the resistance is directly related to the velocity of stretch. He also demonstrated a decrescendo tension in the isometric state at the end of the stretch which is clinically imperceptible; he termed this the "curve of decontraction" and implied that it is due to afterdischarge. This decline in tension in the isometric state after stretch can be recorded quickly and easily in the calf muscles using simple apparatus and only manual fixation of the knee, and the method can be employed in children under the age of 4, an age at which one can be clinically certain that no fibrous contracture is present. The principle is to apply an approximately constant stimulus in the form of dorsiflexion of the foot from its resting position to the right angle within a period of one second. This thrust was originally delivered through scales of the spring-balance type, registering either 0-10 or 0-20 pounds (Fig. 1). The operator sits in such a position that he can see neither the dial of the scales nor the clock; his task is to dorsiflex the foot and then keep it at a predetermined angle by eye for the next 30 seconds, during which time an electrically driven camera records the readings on the two dials and checks against the protractor that the angle of dorsiflexion is in fact constant. At the end of 30 seconds the foot is allowed to return to its original position for a rest period of similar length, and then the procedure is repeated. Any number of recordings can be made at 30-second intervals. After development of the film all the readings for tension and time are plotted as a tension-time curve. An electrical transducer devised later proved somewhat less accurate than the spring balance, but had the advantage that its signal could be recorded simultaneously with the integrated electromyogram of the calf muscles (Fig. 2). The result by either method is a series of exponential curves (Fig. 3), the peak occurring at the moment the foot reaches the right angle and stretching ceases. Even if the procedure is repeated at intervals of half an hour the shape and height of the curves are unchanged and it can be demonstrated that the tonic neck reflexes have no influence on

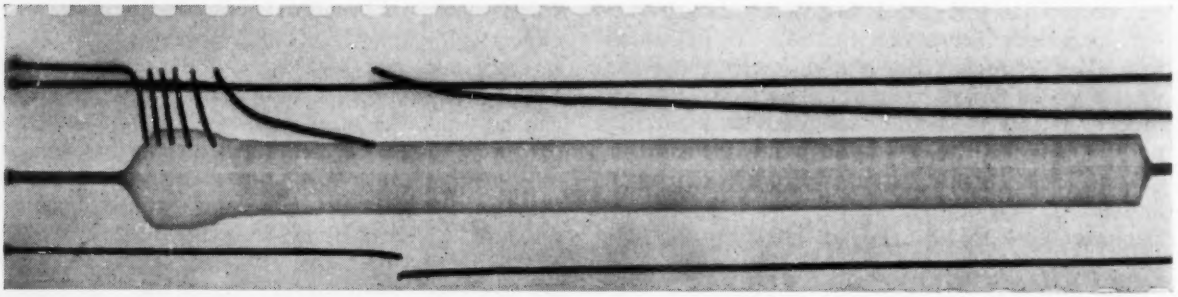

FIG. 2.—Spastic diplegia: calf muscle. Integrated E.M.G. (top trace), E.M.G. of calf muscle (second trace), and transducor signal (middle trace) during isometric stretch for 30 seconds after dorsiflexion of the foot.

muscle tone in the calf measured in this way. Though reproducible results are obtained at any given session, there is considerable variation in the tension recorded on the same child in successive weeks or months.

The curves for a normal adult and two normal children are shown in Fig. 4, from which it is plain that tone as measured in this way depends largely on the bulk of the muscle. If, in a child with spastic diplegia, the calf muscle voluntarily or involuntarily contracts during the declining phase of the curve, it causes only a transient deflection with a quick return to the original exponential curve (Fig. 5). Fig. 6 shows similar sharp deflections, caused by coughing, interrupting the flatter part of the curve, the important feature being that the tension drops from its peak abruptly and does not set off another exponential curve. This is the second clue to the purely physical component of tone.

If the speed of the initial stretch is varied, a family of curves is obtained, the height of the peak being proportional to the velocity of dorsiflexion, as would be expected (Fig. 7). From these curves it is clear that the tension after 15 seconds is quite independent of what has gone on before, that is, whether there has or has not been a peak. One must use the term peak and not "stretch reflex" because the assumption that the peak of tension on sudden dorsiflexion is due to a stretch reflex is not entirely warranted.

The independence of the tension and the velocity of stretch at any period after the first few seconds is the third clue to the physical component of muscle tone recorded in this fashion. The curve is exponential in character, in which case, if the time-base is prolonged, its shape should be preserved, which is in fact the case, as can be seen from Fig. 8. In this instance the isometric stretch was maintained for nine minutes instead of 30 seconds, readings being made every 15 seconds instead of every 2·5 seconds, the integrated electromyogram of the calf muscles being recorded simultaneously and plotted in arbitrary units. It can be seen that electromyographic activity has virtually ceased by one and a half minutes after the beginning of the stretch. Thus it would appear that part of a uniform curve is associated with electrical activity, while the rest is not; the relationship between the two, therefore, must be indirect. Proof that the stretch reflex is not directly responsible for the shape of the curve has not been possible in the spastic child, in whom temporary denervation is not a feasible procedure, and it was therefore necessary to have recourse to the normal adult, in whom the curve is also exponential. Complete denervation by intraneural procaine has no effect on the shape or height of the curve (Fig. 9), as might have been predicted. It has not been established how long denervation must obtain before clinical flaccidity sets in, but it is believed to be a matter of an hour or thereabouts. Chronic denervation, on the other hand, yields a different picture, the muscle acting merely as a slack spring (Fig. 10). It is plain that although temporary denervation by intraneural block does not affect the curve, muscle activity over a substantial period is necessary for the maintenance of its height and its characteristic shape. It appears that the level of the curve can be raised slightly in the normal adult by exertion (Fig. 11), though this effect may be due in part to congestion in the muscle.

Though it is fairly constant on a given day, the height of the curve in the calf of a diplegic child varies from day to day and week to week, and the method is therefore of no value in following progress. It can, however, be shown that certain physiotherapeutic manoeuvres reduce it significantly. The effect of generalized passive flexion of the trunk and limbs for 18 minutes is shown in Fig. 12, tone being reduced by about half; this affects both the general level and the initial peak. The posture adopted in this case, of course, included full dorsiflexion of the feet, and the effect on the calf muscle is probably mainly that of stretching, though subsequent tests have suggested that the effect of pure stretch of the calf muscle with the leg extended is less marked than that of generalized flexion of the trunk and limbs. The reduction in tone after the manoeuvre is, however, transitory, and the curve regains its initial height and shape within 15 minutes.

These results raise the interesting question whether, after prolonged stretching, the reduction of the initial peak is due merely to the halving of all the values of the curve, or whether there is any true reduction in the amount of reflex activity as the result of prolonged extension. The procedure was therefore repeated using the spring-balance technique, the integrated electromyogram being recorded simultaneously. A base-line of resting activity in the integrated electromyogram was first obtained, after which the test procedure was carried out three times. The calf muscle was then continuously stretched for 15 minutes, after which three more tests were recorded. The electrical activity evoked by the test procedure after the period of passive extension shows a significant reduction (Fig. 13). In Fig. 14 the curves for tension and the electromyographic activity in arbitrary units for the three tests before the period of extension and the three tests immediately following it are plotted out; these show the reduction in tension of 2 or 3 lb. throughout the curves, and the considerable reduction in electrical activity. Prolonged stretching, in effect, alters the responsiveness of the stretch reflex. But since it has

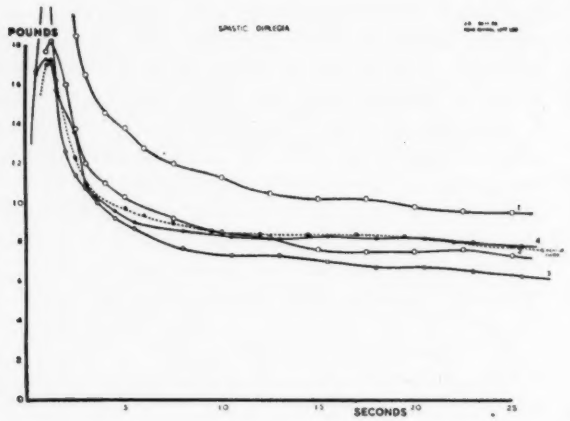

FIG. 3.—Spastic diplegia: calf muscle. Five consecutive tension-time curves recorded at 30-second intervals.

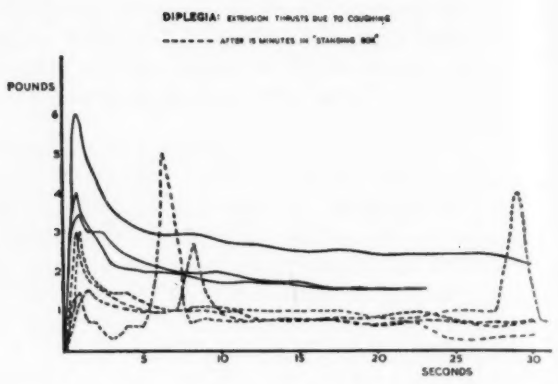

FIG. 6.—Spastic diplegia. Tension-time curves before (continuous lines) and after (interrupted lines) a period of standing with support. The latter curves are disturbed by extensor thrusts caused by coughing.

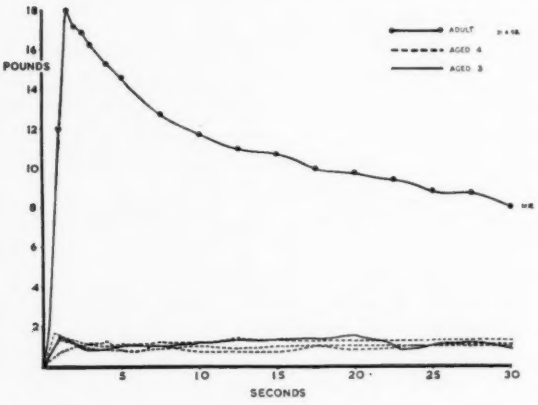

FIG. 4.—Tension-time curves for one normal adult and two normal children aged 4 and 3 respectively.

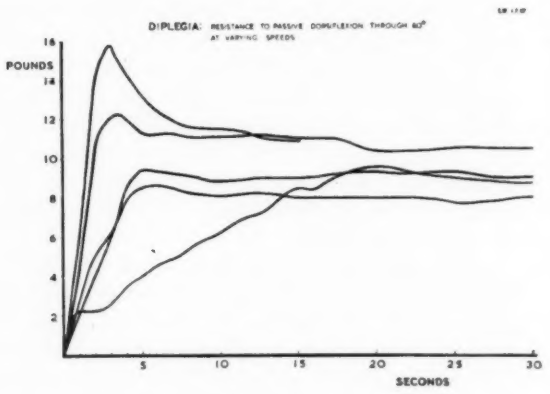

FIG. 7.—Spastic diplegia. Relation between the height of the peak and the velocity of dorsiflexion of the foot.

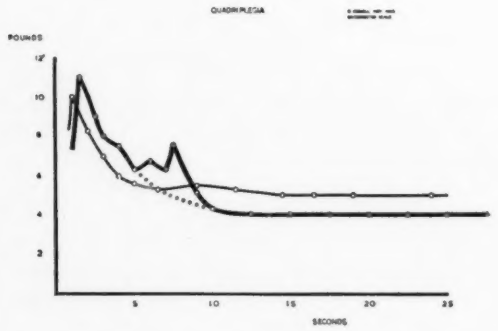

FIG. 5.—Spastic diplegia. Tension-time curves, one being disturbed by an extensor thrust caused by coughing.

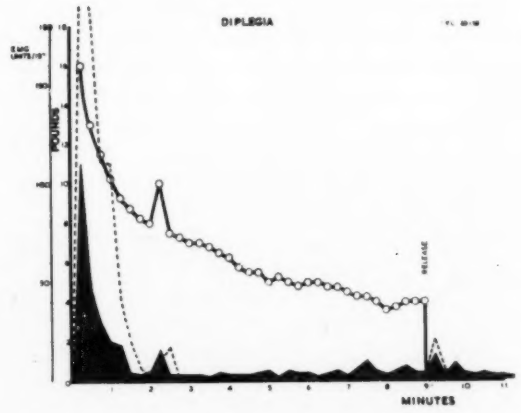

FIG. 8.—Spastic diplegia. Tension-time curve during isometric stretch lasting nine minutes (heavy line). The integrated E.M.G. of the calf muscles is shaded, and the integrated E.M.G. of the anterior tibial group is shown by the dotted line. The curves are disturbed by one involuntary extensor thrust.

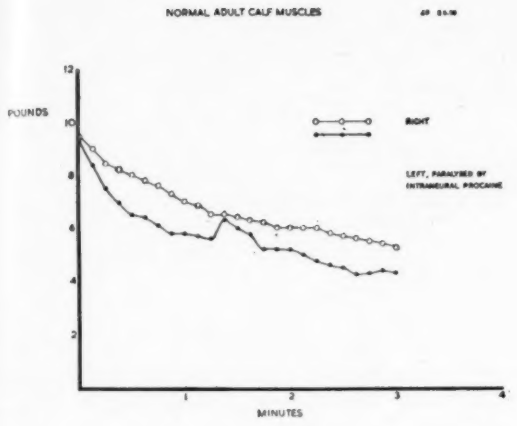

FIG. 9.—Normal adult. Comparison of the curves in the normal right calf (hollow circles) with that of the left calf paralysed by intraneural procaine injection (solid circles). Acute denervation has no effect on the height or shape of the curve.

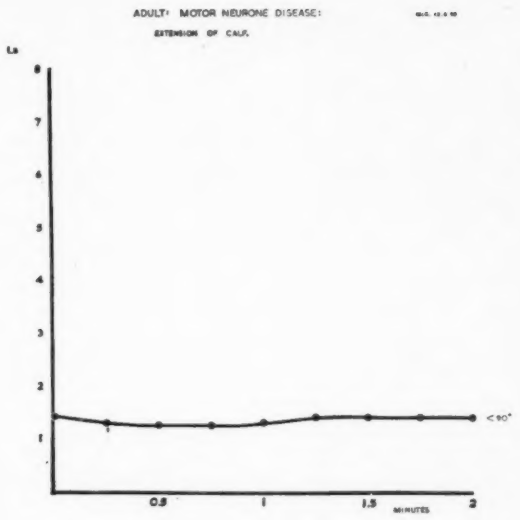

FIG. 10.—Motor neuron disease. The "curve" of a completely denervated calf muscle is flat.

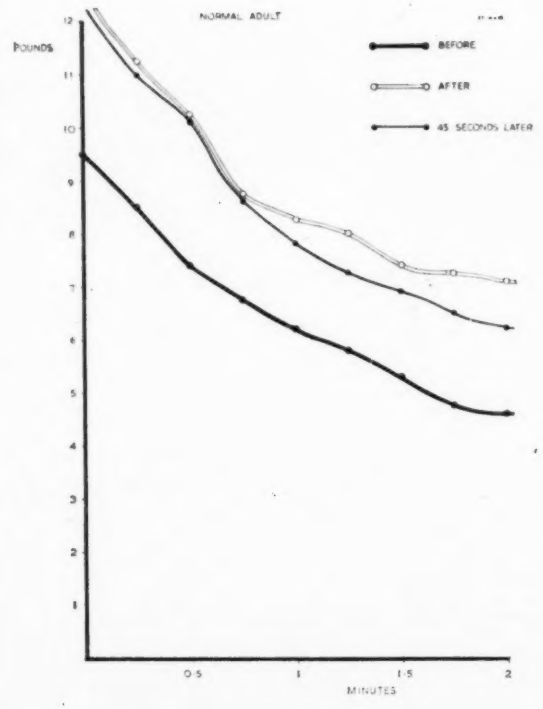

FIG. 11.—Normal adult. Curve before (thick line) and after standing on tiptoes to the point of exhaustion (upper two lines) showing that the tension-time curve can be raised by exertion.

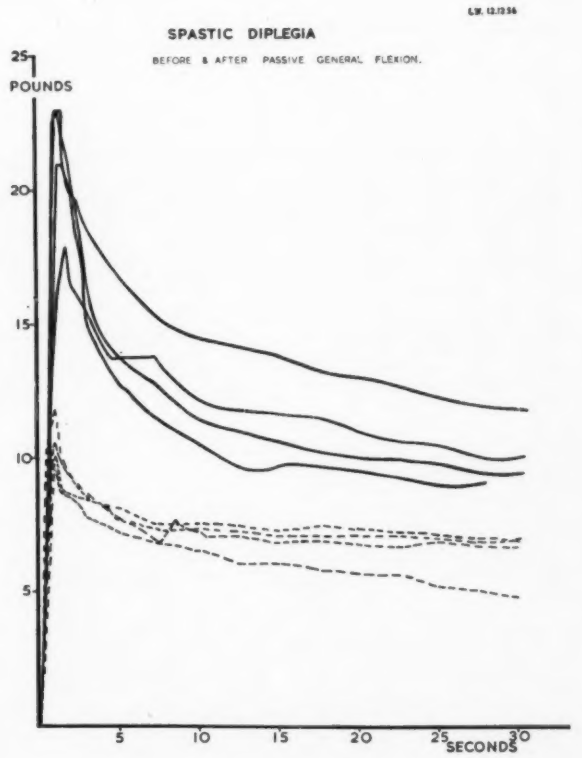

FIG. 12.—Spastic diplegia. Four consecutive tests before (continuous lines) and after (interrupted lines) a period of passive general flexion of trunk and lower limbs for 18 minutes, showing the reduction of "tone".

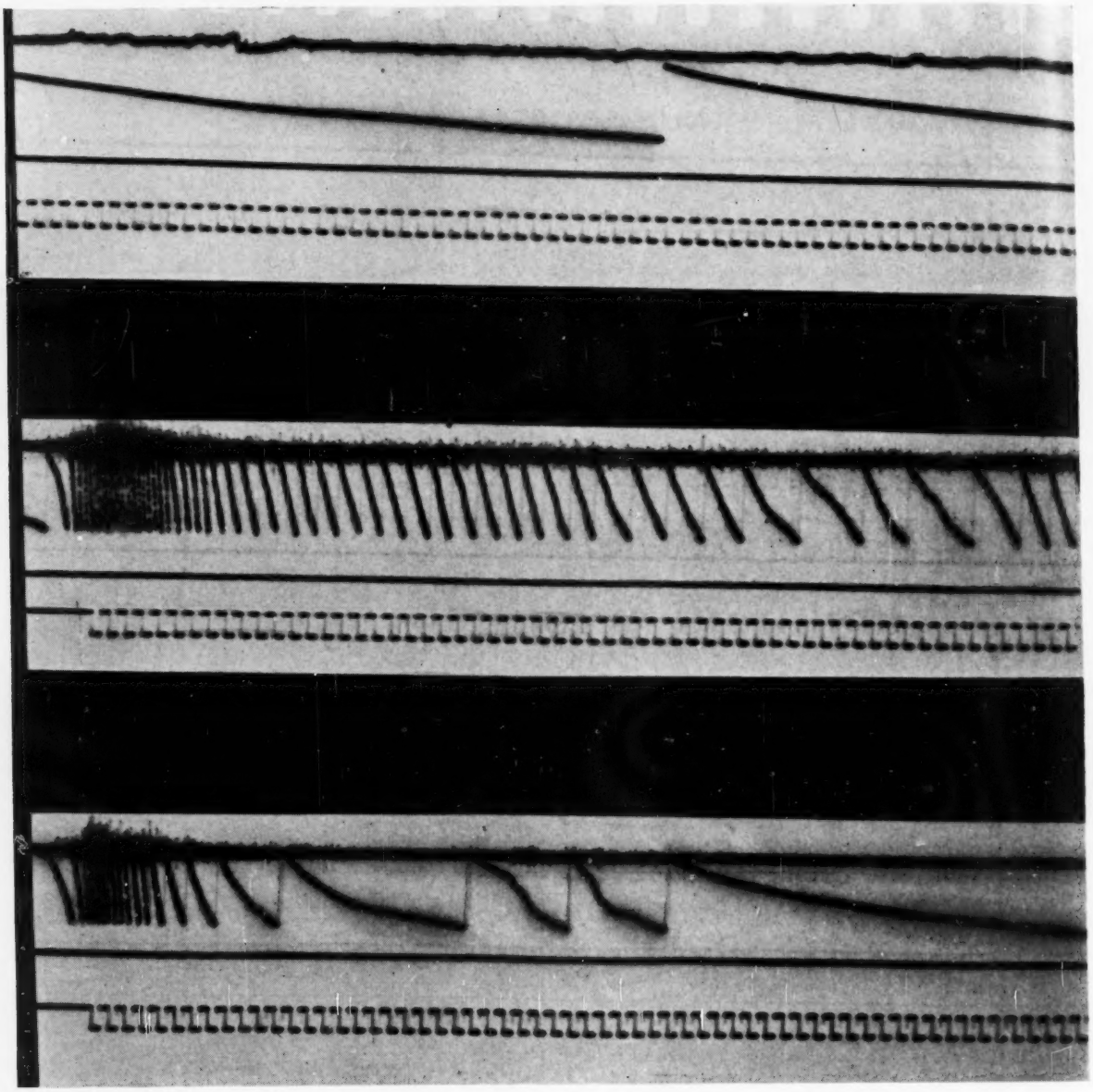

FIG. 13.—Spastic diplegia. Integrated E.M.G. records from calf. Top trace: resting record over a period of 30 seconds; time base 0·5 second. Middle trace: integrated E.M.G. during 30-second period of isometric stretch before period of "treatment". Bottom trace: integrated E.M.G. during 30-second stretch after a period of 15 minutes passive dorsiflexion of the foot, showing the diminution of the tonic stretch reflex.

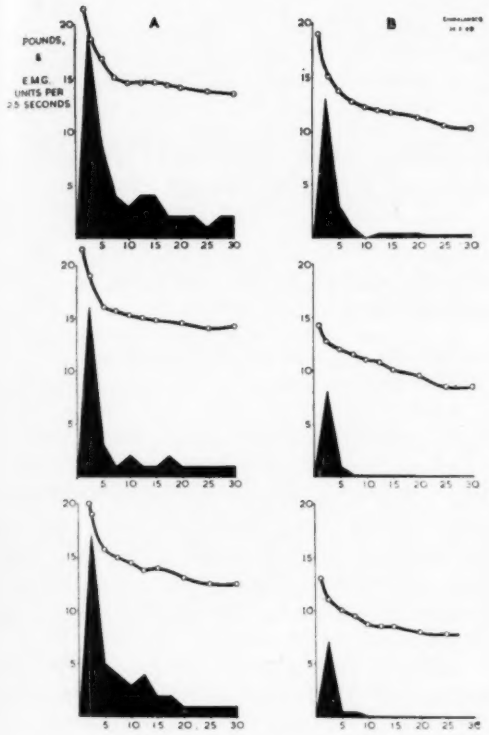

FIG. 14.—Spastic diplegia, the same case as Fig. 13. Column A: tension-time curves (open circles) and integrated E.M.G. units (solid areas) for three consecutive tests before a period of 15 minutes' passive dorsiflexion of the foot. Column B: the same after the period of passive dorsiflexion of the foot, showing the reduction of "tone" and of the E.M.G. response during isometric stretch.

been shown, in the normal at least, that the actual height and shape of the curve is not affected by acute denervation, it would seem probable that the change in the electromyographic activity of a spastic muscle which has been subjected to prolonged extension is secondary to a change in the rheological property of the muscle itself. One visualizes a postural muscle, therefore, as a kind of adjustable viscoelastic springboard, modifiable by prolonged stretching or vigorous activity, the resilience of which is governed, not immediately but over a period of time, by reflex postural activity.

Summary

A simple method of measuring "tone" in the calf muscle of children with spastic diplegia is described. In the isometric state after a stretch, the decline in tension in the muscle follows an exponential curve. The height of the peak of the curve is proportional to the velocity of the initial stretch; although the curve is uniform in shape, electromyographic activity is associated only with its first part, and reasons are advanced for the hypothesis that the actual height and shape of the curve are not directly related to stretch reflex. Prolonged stretching modifies the height of the curve for about 10 minutes, and also indirectly modifies the stretch reflex obtainable from the muscle.

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INTENSE RIGIDITY OF THE ARMS DUE TO ISOLATION OF MOTONEURONES BY A SPINAL TUMOUR

BY

GEOFFREY RUSHWORTH, W. A. LISHMAN, J. TREVOR HUGHES, and D. R. OPPENHEIMER

From the Neurological Research Unit, Churchill Hospital, Oxford, and the Departments of Neurology and Neuropathology, Radcliffe Infirmary, Oxford

In man, persisting muscular rigidity* is usually associated with severe brain damage, as in the decerebrate state and various extrapyramidal disorders. It may also be seen following tetanus. More rarely, cervical cord damage may cause rigidity of the muscles of the arms and shoulder girdle instead of the more usual spasticity. Rigidity of spinal origin is poorly recognized, but recently Penry, Hoefnagel, van den Noort, and Denny-Brown (1960) have reviewed six cases from the literature and have added three examples of their own, including a brief account of the present patient during life. This patient developed intense rigidity in the arms as a result of a spinal neoplasm, and the clinical evolution of this condition will be described, as well as a number of physiological and pharmacological investigations. The results of these indicate a disorder of inhibiting mechanisms which normally control the motoneurones. The undamped discharge of the motoneurones was considered responsible for the maintenance of the severe muscular rigidity. The anatomical findings at death have been compared with the clinical, physiological, and pharmacological data.

The present case differs in certain respects from the others described in the literature. In this patient the rigidity evolved only as his neurological state deteriorated, whereas the previously reported cases were of acute onset, most of them being due to trauma. Furthermore, the distribution of rigidity in this patient was such that the resulting posture of the arms was one of adduction and extension, similar to the quadrupedal decerebrate posture, instead of the more usual abduction and flexion. In spite of the progressive nature of the pathological process (a cervical tumour), there was no detectable change in the physical signs in the upper limbs once the adducted extended posture had become established. The legs, however, passed from normal through spastic paraparesis to spastic paralysis.

The affected muscles were paralysed, and the intense, unremitting rigidity prevented passive displacement of the arms. The rigidity was subject to sudden exacerbations or spasms which gave great pain referred to the neck region. In contrast to spasticity and Parkinsonian rigidity, the paralysis was found to be largely independent of muscle spindle activity, depending instead on the hyperexcitability of alpha motoneurones, and was thus of the "alpha" type described in cats by Granit (1955) and in man by Rushworth (1960). Consequently, attempts to reduce or abolish the rigidity by interference with segmental reflexes were doomed to failure. The electrophysiological studies demonstrated a muscular rigidity due to constantly discharging motoneurones which were at least partially isolated from their nervous connexions, and the pathological features support this view. The rigidity was inaccessible to any form of effective treatment though certain drugs were found capable of modifying it for short periods of time. Its unremitting character, even during natural sleep, and the tendency to severe exacerbations of agonizing spasms were a challenge to our therapeutic and palliative resources in this most distressing, prolonged, and painful condition.

Case Report

A.N., aged 47, was an area youth organizer. He died on July 29, 1960.

Early in 1957 the patient began to experience pain in the back of the neck, sometimes radiating into the upper arms. It was aggravated by coughing or straining. One year later, the fingers of the left hand became numb, and six months after this the left arm was noticed to be weak when swimming, and the left leg felt awkward and caused him to stumble occasionally. Early in 1959 he was admitted for investigation under the care of Dr. Ritchie

*Muscular rigidity is said to be present in a limb when muscles actively resist passive movement of a joint no matter what the direction of displacement. The posture imposed on the limb by rigid muscles partly depends on the size of the opposing muscle groups, and partly on the distribution and reflex accessibility of the motoneurone discharge causing the rigidity.

Russell. Examination then showed that he carried his head slightly tilted to the right. The cardiovascular, respiratory, genito-urinary, and alimentary systems showed no abnormality. The cranial nerves and optic fundi were normal. A left Brown-Séquard syndrome with a sensory level at C3 was present. The proximal muscles of the left arm were slightly wasted, without fasciculation. Gait was unsteady and Romberg's sign was positive.

Routine blood counts were normal. The Wassermann and Kahn reactions were negative. Radiographs of the skull and cervical spine showed no abnormality. Lumbar puncture revealed a complete block, and the cerebrospinal fluid contained 60 mg. of protein per 100 ml. and 3 lymphocytes per mm^3. The Wassermann reaction of the cerebrospinal fluid was negative. Myelography from the lumbar region demonstrated a complete block at the level of the fourth cervical vertebra.

On February 24, 1959, Mr. Pennybacker performed an upper cervical laminectomy and the spinal cord was found to be expanded at the C2 to C3 level to the extent of filling the whole theca. It appeared grayish on the left and the diagnosis of intramedullary tumour was not in doubt. Aspiration did not yield fluid, and no biopsy was taken. The dura was left widely open and the wound sutured.

Post-operatively, the patient's condition remained static for six months, when the right arm became increasingly numb, then weak and stiff. About one month later, numbness of the right leg appeared, and a few weeks later the weakness and stiffness of both arms suddenly and rapidly increased. The condition of the legs was unaltered. Sphincter control was normal except for very occasional dribbling if the bladder became overdistended.

In December, 1959, he was readmitted to the neurosurgical unit. Examination then showed that the cranial nerves and optic fundi remained normal. In the motor system, both arms were rigidly extended and adducted while the forearms were pronated. Voluntary movement was very weak in all muscle groups in the arms. The power in the hands was surprisingly good, but it was impossible for him to abduct the arms or flex the elbow. No fasciculation was observed. Power was almost normal in the legs but was diminished in the proximal muscles. No tendon reflexes could be elicited in the arms, but they were brisk in both legs. The abdominal reflexes were present and equal. A few beats of clonus could be elicited at the left ankle and both plantar responses were extensor. The respiratory movements were somewhat limited.

In the sensory system, the sensation of pinprick was impaired, over the entire body below C3 on both sides, but markedly so from C5 to T1 on the right. The sensations of hot and cold were impaired below C3 on both sides and were totally absent in the right arm. The sensation of light touch was impaired from C3 to T3 bilaterally but was normal below this. Joint position sense was impaired distally in both arms, the right being worse than the left, and vibration sense was absent below the neck on both sides. Stereognosis was impaired in both hands.

FIG. 1.—The patient standing, four months before his death, showing the fixed posture of the arms and shoulder girdle.

On December 31, 1959, Mr. Pennybacker re-operated and tumour was apparent throughout the cervical enlargement, but was greatest opposite C3, C4, and C5. A longitudinal incision 4 cm. long was made in the left posterior column of the spinal cord and a firm pinkish mass was encountered at a depth of less than 1 mm. This was shelled out without difficulty, except for adhesions to the white matter at the upper pole. It was an apparently circumscribed, histologically benign, astrocytic tumour weighing 2 g. The dura was left open and the wound sutured.

Post-operatively, the weakness of the arms had increased distally, especially on the left, and the spinothalamic sensory deficit had extended to involve the whole of the right side of the body, where it was extremely dense. The condition of the legs was unchanged.

When the patient again came under the care of the neurological unit in March, 1960, there was little change in his condition, the most striking feature being the intense spasm of shoulder and arm muscles which imposed on the upper extremities the posture of adduction, internal rotation, extension, and semipronation. The shoulders were drawn forward, and the head tilted to the right (Fig. 1). In spite of a mild spastic paraparesis worse on the left, he was able to stand and to walk quite well with support. The abnormal posture of the

arms persisted unchanged until his death from bronchopneumonia four months later. During this time movement at the fingers and wrist became progressively impaired and the muscles rigid, fixing the wrist in extension and the fingers in flexion. The spastic paraparesis gradually progressed to complete spastic paraplegia and respiratory movements became weaker.

Electrophysiological Observations.—Three months before his death simultaneous recordings of the electrical activity of, first, the right deltoid and pectoralis major muscles, then the right biceps and triceps muscles were taken using coaxial needle electrodes in the muscles and a balloon over the operative joint to signal movement there. (For details of methods see Rushworth, 1960.)

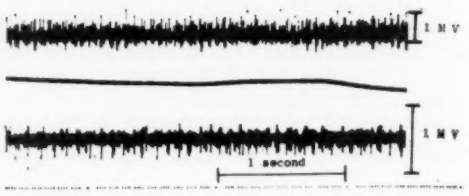

FIG. 2.—Electromyogram recordings from the right deltoid muscle (upper line) and the right pectoralis major muscle (lower line). Mechanogram (middle line) from a balloon over the pectoralis major to signal movement at shoulder joint. Spontaneous activity.

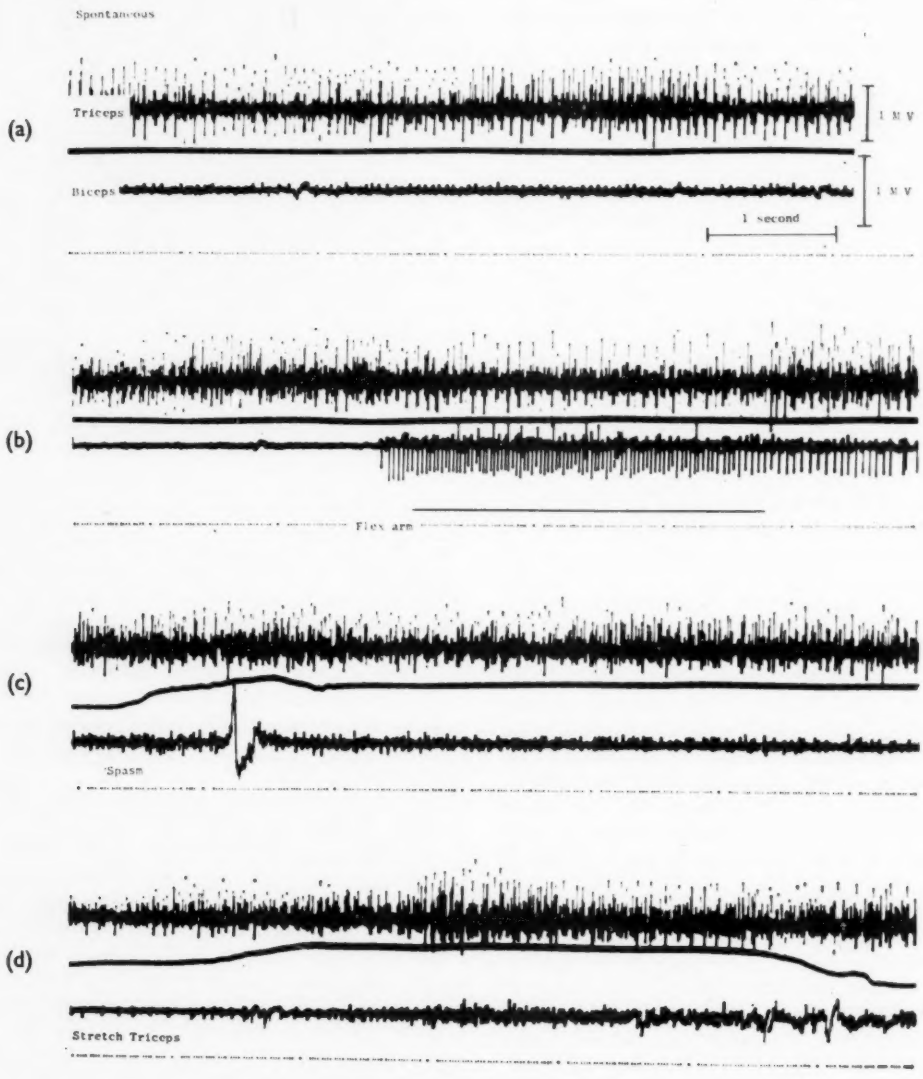

FIG. 3.—Electromyograms from the triceps (upper line) and the biceps (lower line). (a) Spontaneous activity; (b) attempt to flex arm produces single unit response in the biceps and some inhibition of the triceps discharge; (c) a spontaneous spasm evokes an increased firing rate in both triceps and biceps; (d) passive stretch of the triceps has at first little effect until a spasm in both triceps and biceps supervenes.

Deltoid and Pectoralis Major.—The spontaneous activity in both these muscles was intense, with many motor units firing at rates up to 20/sec. (Fig. 2). This was not influenced by painful stimulation of the skin or by passively turning the head and neck. When the pectoralis muscle was stretched by attempted passive abduction of the arms, there was a considerable increase in the electrical activity of this muscle and also in its anatagonist, the deltoid. This was similar to the stretch response described below for the triceps muscle (Fig. 3d). It was not a true stretch reflex because the muscle response did not appear as soon as the muscle was stretched but occurred suddenly during stretching, and with a simultaneous outburst in its antagonist. The burst of activity in the pectoralis muscle was so great that the limb became firmly adducted again. This activity did not cease when the muscle shortened, but slowly decreased over several minutes. In these features it resembled the spasms which occurred spontaneously from time to time.

When the patient attempted to abduct the arm there was very little increase in the motor unit discharge of the deltoid, but the pectoralis responded with an outburst of activity which was almost as great as when the patient tried to adduct the arm voluntarily.

Following a xylocaine injection around the brachial plexus by the method of Lookman (1958), the stretch response and voluntary activity were gradually blocked simultaneously. When the block was maximal it was quite easy to abduct the arm passively to 90° before considerable resistence was met (presumably contracture). Before injection 15° of passive abduction always met with overwhelming resistance.

Biceps and Triceps.—A great deal of spontaneous activity was recorded in these muscles (Fig. 3a) which was greatest in the triceps muscle where several motor units were discharging at about 15/sec. In the recordings from the biceps muscle, a small single motor unit was also discharging at about 15/sec. This spontaneous activity was surprisingly constant for long periods of time, but there were occasional bursts of increased firing simultaneously in the two muscles associated with a spontaneous painful spasm (Fig. 3c). The discharge rate during the spasm was about twice that of the steady spontaneous activity and it took several minutes to resume the lower rate again. At no time were excessively high discharge rates observed, and it was not possible to influence the motoneurone discharge either by passively turning the head and neck, or by painful stimulation of the fingers.

In spite of the clinical impression that no voluntary activity was present in these arm muscles, the electromyogram of the biceps showed a single unit discharge when the patient was asked to try to flex his arm (Fig. 3b). During the biceps discharge, the spontaneous discharge rate in the triceps was slowed, a few motor units even being completely inhibited. The ending of the contraction of the biceps was heralded by a deceleration of the single motor unit recorded in that muscle, and by a burst of increased activity in its antagonist. No voluntary activity was seen in the triceps.

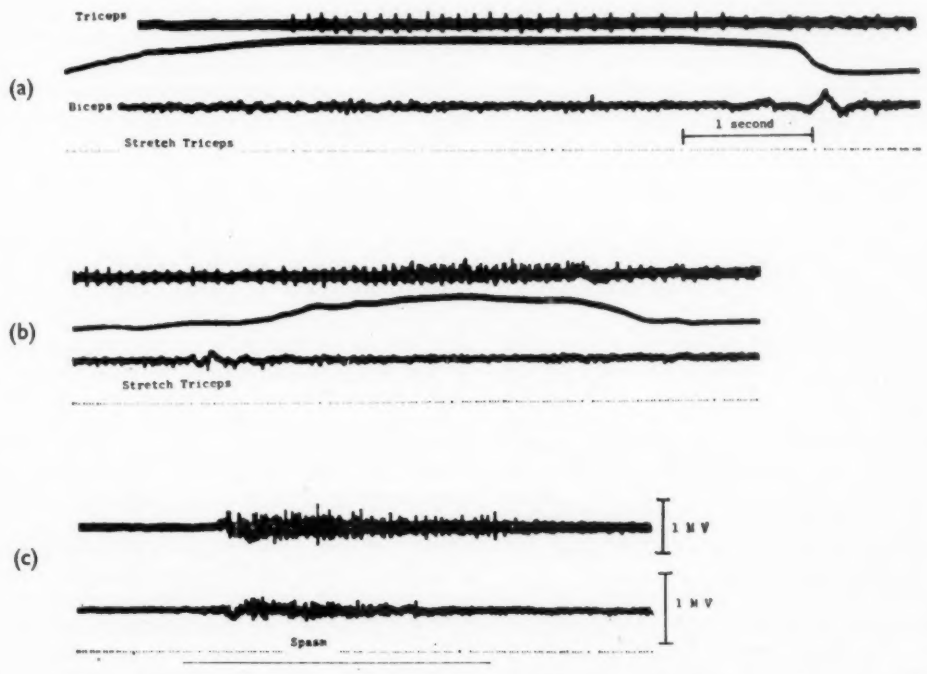

FIG. 4.—Five minutes after the procaine injection. (a) No spontaneous activity in the triceps, but a single unit is evoked by passive stretch; (b) repeated passive stretch produces a greater response, this being the fifth repeated stretch response; (c) a spontaneous spasm shows that the triceps is still innervated but much less than previously.

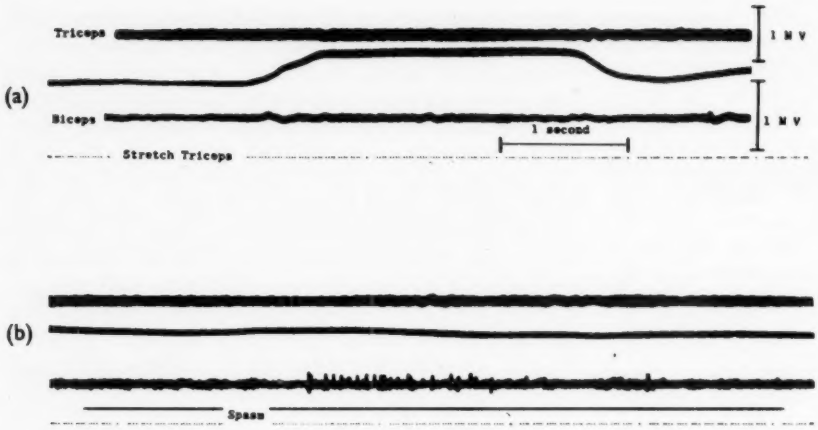

FIG. 5.—Ten minutes after the procaine injection. (a) The stretch response of the triceps is absent and there is no spontaneous activity; (b) a spasm shows that the triceps is now denervated by the local anaesthetic.

The response of the triceps muscle to slow stretch (Fig. 3d) added little at first to the spontaneous activity in this muscle, but continued stretch eventually evoked a spasm in both the triceps and biceps muscles which was not interrupted by relaxation of the stretching stimulus. There appeared, therefore, to be very little true stretch reflex in the triceps muscle.

The injection of 10 ml. 2% procaine near the motor points of the triceps muscle produced, almost at once, reduction of the spontaneous discharge of motor units in that muscle. Only three units fired spontaneously and the discharge rate of one of them was about 9/sec. Spontaneous activity in the biceps continued, of course, at its previous rate. Stretching the triceps muscle produced only a small stretch reflex with increased activity also in the antagonist. The spontaneous activity of the triceps could be completely inhibited by efforts to contract the biceps muscle, which in fact could now bring about slight flexion of the arm. On ceasing the attempt to flex the arm the spontaneous activity of the triceps returned and accelerated; only two motor units were, however, active.

Five minutes after the procaine injection (Fig. 4) the spontaneous activity had completely disappeared, but by stretching the triceps muscle, a single unit response could be obtained (Fig. 4a). Repeated stretches brought back a background of spontaneous activity, and by the fifth successive stretch four motor units were responding (Fig. 4b). Presumably, therefore, the triceps motoneurones were still susceptible to post-tetanic potentiation from muscle-spindle afferents. A spontaneous spasm affecting both biceps and triceps occurred (Fig. 4c) and this showed that the triceps muscle was still partly innervated, though some motor nerve fibres were clearly blocked by procaine as the motor unit discharge was much less than before the injection.

Ten minutes after the injection of procaine (Fig. 5a) there was no spontaneous activity in the triceps and no stretch response. During a spasm, the triceps muscle no longer responded (Fig. 5b) and was now completely paralysed by the local anaesthetic.

It is apparent, therefore, that the small stretch reflex of the triceps muscle in this patient persisted until it was paralysed by the procaine. These facts make it very unlikely that hyperactive muscle spindles were responsible for the rigid state, for they would have produced a characteristic stretch reflex which would begin immediately the muscle was lengthened and cease when it was allowed to shorten. Furthermore, gamma motor fibre activity, which can cause muscle spindle hyperactivity and the exaggerated stretch reflex of spasticity, is particularly sensitive to procaine and is thus blocked before other reflexes or voluntary activity (Matthews and Rushworth, 1957; Rushworth, 1960). This rigidity is, therefore, of the "alpha type" (Pollock and Davis, 1931; Granit, 1955), which in animals is unaffected by dorsal root section and is believed to depend principally on the hyperexcitability of the motoneurones themselves or by an imbalance of facilitatory and inhibitory mechanisms acting on them.

The studies of the pectoralis and deltoid muscles showed a considerable disorder of the reflexes acting on antagonists (reciprocal innervation). The vast amount of spontaneous activity and stretch responses (which were no more sensitive to local anaesthetic than was the voluntary activity of the muscles) showed that the muscular rigidity was of the alpha type due to hyperexcitability of the motoneurones themselves and independent of local reflexes.

Few surviving motoneurones of the deltoid and biceps could be excited by voluntary effort, and they were not activated by painful stimulation of the skin and turning of the head and neck. Passive stretch of the triceps muscle had little effect on the intense spontaneous motoneurone discharge, and voluntary effort had none. Pectoralis motoneurones could be excited by voluntary effort, but only a little by other excitatory afferents, and they could not be inhibited by attempted contraction of the antagonistic muscle. These facts lead one to believe that the intrinsic cord lesion causing these disorders was probably one interfering with the connexions of the interneurones which are so very much concerned with the segmental interplay of reflexes as well as connected with the many supraspinal and intersegmental influences finally inpinging on the motoneurones.

Therapeutic Trials.—Rational means of alleviating the alpha type of rigidity will depend on methods for decreasing or removing factors which are known to stir up the motoneurones, or they will attempt to interrupt or reduce the discharge at some point in the final common pathway to the affected muscle. They are very limited, but the following procedures were tried:

Repeated passive movements were attempted but were defeated by the pain produced (in spite of analgesics) and by the intensity of the spasm at all joints other than the fingers and wrist. Heat applied by an electric blanket lessened spontaneous pain but not the rigidity. Prolonged splinting with elbows in flexion produced no benefit, and gentle traction to draw the arms away from the trunk could be tolerated for only a few minutes at a time.

A sphygmomanometer cuff was inflated to 180 mm. mercury for 25 minutes in order to render the nerves and muscles of the limb ischaemic, and for half an hour afterwards there were fewer spontaneous spasms and finger movements were freer.

Mephanesin elixir was given orally in doses up to 1 g. four-hourly without demonstrable effect.

Chlorpromazine was given intravenously in a dose of 50 mg. with considerable diminution in the rigidity of all muscle groups for four to five hours afterwards. Sudden passive movements of the joints still induced severe painful spasms, however. An oral dose of 150 mg. four times a day slightly decreased the rigidity, but the effect diminished after two or three days.

Sodium thiopentone (Pentothal) was given intravenously in a dose just sufficient to depress respiration, and it immediately produced considerable relaxation of rigidity, and 50 mg. of succinyldicholine chloride (Scoline) intravenously maintained the relaxation. When the effect of the Pentothal and Scoline had worn off, 90 mg. of gallamine triethiodide (Flaxedil) was given intravenously almost completely relaxing the rigidity for 30 minutes. Spasm in response to sudden movements returned before the constant rigidity, and for three hours afterwards the patient was able to tolerate flexion of the left elbow almost to a right angle.

D-tubocurarine chloride (Curare) was given intravenously in a dose of 5 mg. without general anaesthesia. This produced immediate and considerable relaxation of rigidity, and no spasms occurred for half an hour. The effect wore off gradually over the course of five hours. Ten minutes after the injection, when relaxation was maximal in the arms, it could be demonstrated that power was unaffected in the legs or trunk.

Ten millilitres of 20% magnesium sulphate solution, were injected slowly intravenously, and had no effect on the rigidity but made the patient sleepy.

Ten millilitres of 20% calcium gluconate solution were injected slowly intravenously and had no effect.

Chlorothiazide, 0·5 g. twice daily, was given orally without potassium supplements for five days in order to lower the serum potassium level. This fell to 3·1 mEq./litre for three days during which there was depression of the ST segments in the electrocardiogram. No effect was noted on the rigidity or spasms.

Two per cent procaine hydrochloride was infiltrated extensively into the triceps and biceps muscles of one arm with some relief of rigidity for half an hour. Infiltration of the lateral and posterior cervical muscles lessened their rigidity for several hours during which the spontaneous painful spasms of the arms were considerably reduced. Finally, procaine block of the brachial plexus by the method described by Lookman (1958) was repeatedly shown to abolish rigidity for periods up to two hours.

Thus the agents found to modify this patient's rigidity were chlorpromazine, thiopentone, depolarizing and anti-depolarizing relaxants, and procaine. Unfortunately, none acted in a way which was of significant therapeutic benefit.

Pathology.—Necropsy was performed 28 hours after death (Radcliffe Infirmary, Oxford, P.M. No. 627/60). Abnormal findings were confined to the respiratory, nervous and muscular systems.

Respiratory System.—The immediate cause of death was an extensive bilateral bronchopneumonia, obvious macroscopically and confirmed histologically.

Nervous System.—The brain weighed 1,400 g. and appeared normal externally. No abnormality was seen in centimetre coronal slices of the cerebrum, and histological sections of the cerebellum, pons, and upper medulla showed no changes. The changes in the lower medulla will be described with those of the spinal cord.

The spinal cord was removed in two pieces: an upper portion, comprising segment C1 to T6, within the vertebral column and post-vertebral muscles, and a lower portion removed in the usual way from the spinal canal, which here showed no abnormality.

The upper portion was dissected after fixation. There had been a laminectomy of the second to sixth cervical vertebrae. The overlying muscles had healed by fibrous scarring without suppuration. Deep to these muscles was a cavity, measuring 10 cm. from above down and 3 cm. transversely, filled with clear fluid and lined by a glistening membrane. Projecting into this cavity from the posterior aspect of the third, fourth, and fifth cervical cord segments was a soft pink tumour mass about 2 cm. in diameter. The dura was deficient in this region. Anteriorly, the cord from C2 to C6 was flattened and expanded, especially on the left. The emerging roots and ganglia appeared normal, and the leptomeninges showed no sign of tumour infiltration. In transverse sections, the cord at level C1 was expanded and the normal gray-white demarcation was preserved. Segments C2 to C6 were distorted and expanded by tumour, and it was not possible to distinguish macroscopically between grey and white matter, or between nervous and tumour tissue. At C7, the normal cord pattern re-emerged, and from T1 downwards the cord looked normal.

Histology of Spinal Cord.—Transverse blocks from each cervical segment and from the first and tenth thoracic and second lumbar segments were embedded in paraffin wax and sections stained for nerve cells, nerve fibres, myelin, and neuroglia. A block from T8 was stained by the Marchi technique. Frozen sections were

cut transversely from C3 and stained to demonstrate lipid, axons, astrocytes, and microglia.

The histological appearance of the tumour differed strikingly from that of the mass removed from the posterior columns seven months before death. The earlier specimen showed no signs of malignancy; it consisted of a dense feltwork of glial fibres mixed with astrocytes and Hortega cells. Numerous small, thick-walled vessels were present, many showing dense lymphocytic cuffing (Fig. 6). No nerve cells or nerve fibres were seen.

The tumour found at necropsy was a diffuse cellular astrocytoma extending from the lower medulla (at the level of the obex) down to the eighth cervical segment. The extent of tumour infiltration is shown in Fig. 7. Infiltration was most intense in the gray matter, and at the upper and lower limits of the affected region it was practically confined to the gray horns. The tumour showed regional differences; parts were pilocytic, others fibrillar, others gemistocytic (Fig. 8). In the infiltrated gray matter, surviving neurones were seen, and in the white matter, although myelin had disappeared, there were numerous axons threading their way between the tumour cells.

An area of malignant change was present on the left, extending between the segments C2 and C6. The appearance at C2 is shown in Fig. 9. Here the picture was that of a pleomorphic glioblastoma, with giant cells (Fig. 10). Tumour had destroyed and replaced the left posterior horn and posterior and lateral columns, and by its expansion had produced severe distortion of the remaining cord.

The myelin and Marchi stains showed Wallerian degeneration corresponding to a cord transection complete on the left side, incomplete on the right. The effects were seen in the lower medulla and C1 segment as degeneration of the cuneate and gracile tracts and of the left spinocerebellar tracts. Below the tumour, the pyramidal tracts were degenerate, the left one completely so.

Cervical Cord Neurones.—The pattern of cell loss and cell damage in the anterior horns and intermediate gray matter is of especial interest in this case. Unhappily, the estimation of these features is to a large extent subjective. Whereas large motor cells may be readily recognized and their severe depletion be apparent, it is less easy to recognize moderate cell loss in a grossly distorted cord infiltrated with tumour. As to the smaller nerve cells, it is often impossible to decide whether their appearance is normal or pathological; whether, for instance, a particular cell should be described as "small and dark" or "shrunken and pyknotic". In some areas, even the distinction between neurone and astrocyte is doubtful. The description which follows should be read with these reservations in mind.

In sections from the lower medulla, the nerve cells of hypoglossal and supraspinal nuclei appeared intact, in spite of slight tumour infiltration. Motor cell loss was first apparent in the lower part of the first cervical segment, the loss being greatest on the right. Both anterior horns were grossly depleted from C2 to C6, and no motor cells were seen on the left in segments C4 and C5. From C7 downwards the anterior horns contained motor cells in normal numbers (see Table).

TABLE

EXTENT OF MOTOR CELL LOSS IN SEGMENTS OF CERVICAL CORD

Level	Right	Left
C1	Slight	Slight
C2	Severe	Severe
C3	Severe	Severe
C4	Severe	Total
C5	Severe	Total
C6	Slight	Severe
C7	None	Slight
C8	None	None

The smaller nerve cells of the intermediate and posterior gray matter could be distinguished in the upper and lower cervical segments on both sides. In the more affected segments, they were reduced in number or absent but the presence of tumour made reliable counts impossible.

The morphology of the motor cells in the tumour-infiltrated horns was abnormal. The most striking change was a rounding-off of the cell outline, and loss of dendrites. The remaining dendrites were usually tenuous and they stained feebly (Figs. 11 to 15). This change seemed significant, as the motor cells of the hypoglossal nucleus and of the anterior horns below the tumour showed normal antler-like expansions.

Spinal Nerve Roots. Posterior Root Ganglia, Peripheral Nerve, and Muscle.—The anterior roots showed loss of fibres corresponding to the loss of cells in the cervical cord segments, as described above. The posterior roots and their ganglia showed no change. The tumour had not extended along the nerve roots.

Silver impregnation of peripheral nerve supplying muscles of the upper limbs showed variable numbers of axons undergoing fragmentation.

The following muscles were examined: Tongue, right and left sternomastoid (C1-5), diaphragm (C3-5), right and left deltoid (C5-6), right and left pectoralis major (C5-T1), left biceps brachii (C5-6), right palmaris longus (C8), right and left lumbricals (C8-T1), and rectus abdominis.

As might be expected, the tongue and rectus abdominis showed no abnormalities. All the other muscles examined showed atrophy indicative of recent partial denervation (Fig. 16). Many of them also contained scattered interfascicular inflammatory foci, consisting of lymphocytes, neutrophils, and monocytes (Fig. 17). These inflammatory changes are most plausibly attributed to mechanical damage due to prolonged spasm.

In relating the pathological to the clinical features of this case, it has to be remembered that the pathological description refers to the patient's final state, whereas most of the physiological observations refer to a period four months earlier. It is not known when the spinal tumour underwent malignant

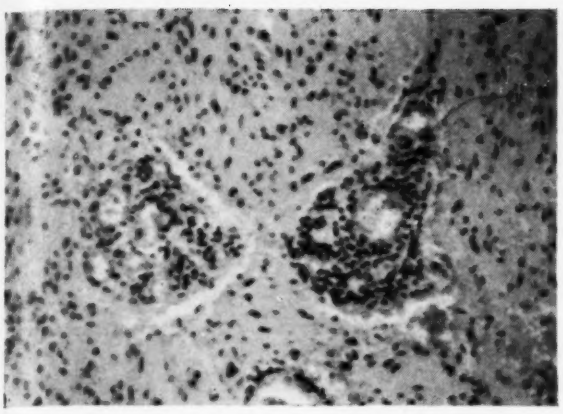

FIG. 6.—Section of intramedullary astrocytoma removed seven months before death. Similar astrocytic and vascular profileration was present in areas of the tumour examined at necrospy. Haematoxylin and eosin × 133.

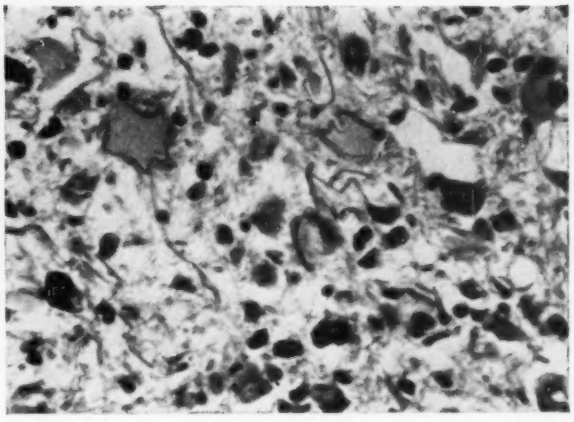

FIG. 8.—Transverse section of spinal cord segment C4 showing gemistocytic astrocytoma. Phosphotungstic acid haematoxylin × 310.

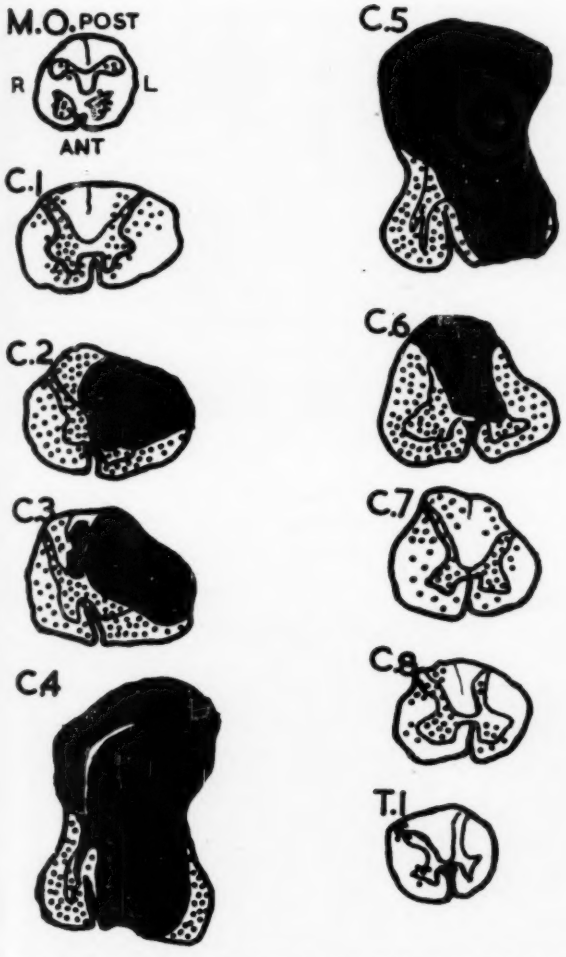

FIG. 7.—Diagrams from camera lucida tracings of histological preparations illustrating the changes in the cervical cord at successive levels. Stippling indicates infiltration of nervous tissue by astrocytoma. Solid black indicates destruction of nervous tissue and replacement by malignant tumour × 2. Seen from upper surface; the left side of the cord is on the right of each diagram.

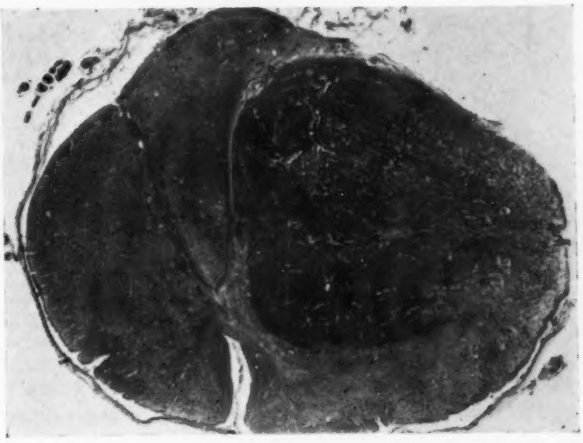

FIG. 9.—Transverse section of spinal cord segment C2 showing malignant tumour (glioblastoma) on the left. The remaining cord here is infiltrated with astrocytoma. Holmes × 4.

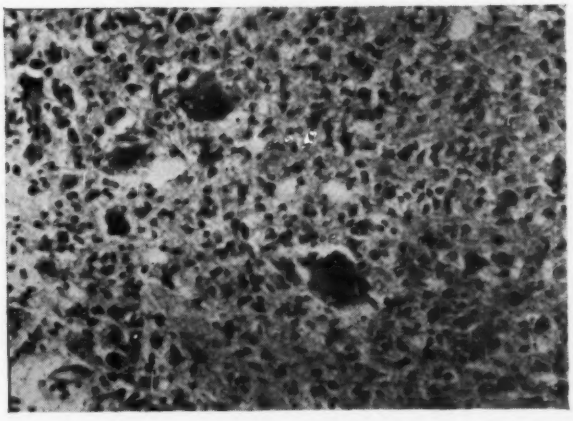

FIG. 10.—T.S. of C4 showing malignant tumour (glioblastoma). Haematoxylin and eosin × 133.

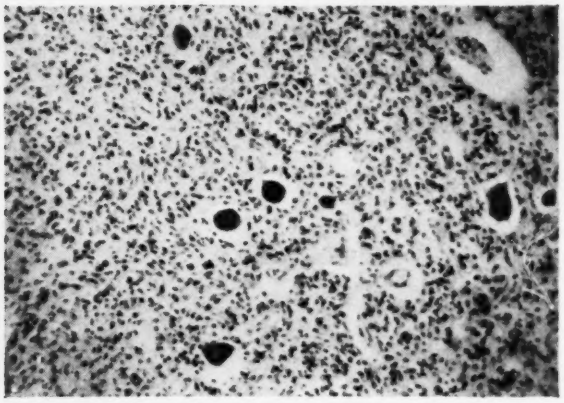

FIG. 11.—T.S. of C6 showing astrocytoma surrounding surviving motoneurones in the anterior horn. Nissl. × 80.

FIG. 12.—Motoneurone from anterior horn of C2. Note rounding of contour and absence of dendrites. Glees. × 310.

FIG. 13.—Normal motoneurone from C1. Glees. × 310.

FIG. 14.—Motoneurone from anterior horn of C6. Note frail dendrites. Nissl. × 310.

FIG. 15.—Normal motoneurone from T1. Nissl. × 310.

FIG. 12

FIG. 13

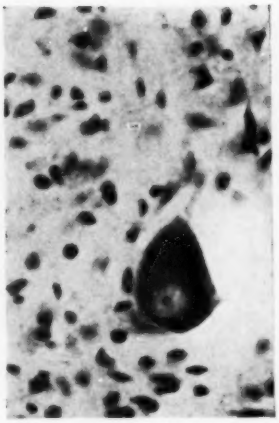

FIG. 14

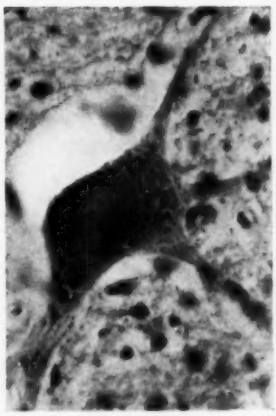

FIG. 15

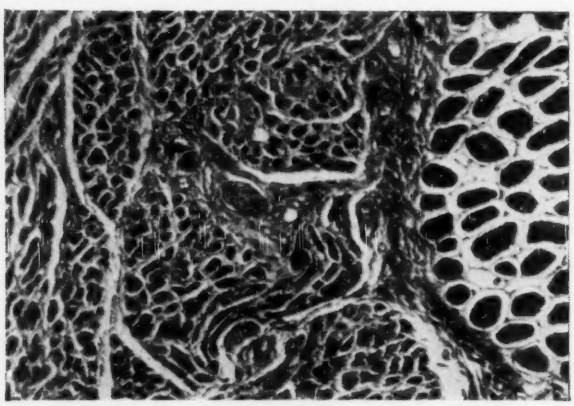

FIG. 16.—T.S. of right palmaris longus showing muscle atrophy. Haematoxylin and Van Gieson. × 50.

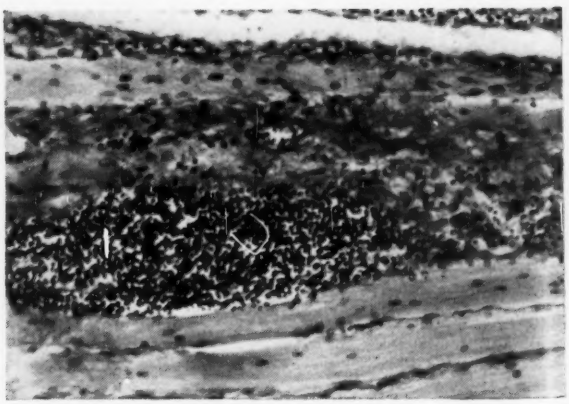

FIG. 17.—L.S. of a lumbrical muscle showing marked inflammatory reaction. Haematoxylin and Van Giesen. × 80.

change; but it is reasonable to suppose that the patient's muscular symptoms were due to the relatively slow infiltration of the anterior horns by astrocytoma, isolating without destroying the motor cells, and that the massive destructive lesion seen in segments 4 to 5 represents a late malignant development, which would ultimately substitute a flaccid paralysis for the previous muscular overactivity.

Discussion

Thorburn (1887) first clearly described the characteristic abnormal posture of the upper limbs which may result from trauma of the cervical spinal cord. Since then, this posture of rigid abduction and external rotation of the arms, with flexion of the forearms and drawing forward of the shoulders, has been recognized as a sign of severe cord injury at about the C6 segment. It has often been attributed to the unopposed activity of unaffected muscles innervated by the C5 segment but this explanation has been challenged by Penry *et al.* (1960).

In our own case, the posture of the arms was similar to the decerebrate posture, the arms being adducted and extended. Although there was some voluntary activity in the pectoralis major, it was the large amount of spontaneous activity which kept the arms in the adducted posture. The extension of the arms was similarly maintained by the intense spontaneous activity of extensor motoneurones, such as those of the triceps, over which there was no voluntary control. It seems probable, therefore, that it is the intensity and distribution of the spontaneous activity of motoneurones giving rise to muscular rigidity which finally determines the posture.

Spasticity and Parkinsonian rigidity in man are disorders of the stretch reflex mechanisms, and the basic defect lies in the overactivity of the motor supply of the muscle spindles ("gamma rigidity") (Rushworth, 1960). As a consequence, the afferent discharge in response to stretch is out of proportion to the stimulus and a large stretch reflex results. This can be abolished by anaesthetizing the gamma motor fibres by injecting procaine intramuscularly or partial nerve block, for these fibres are particularly sensitive to local anaesthetic. Among 50 cases, Rushworth found only one spastic case which did not fit into this category. In this case, the stretch reflex could not be selectively reduced by procaine but persisted until the muscles themselves were paralysed. In these features the spasticity resembled the alpha rigidity of the anaemically decerebrated cat (Granit, 1955) which is not abolished by dorsal root section (Pollock and Davis, 1931) or local anaesthesia (Matthews and Rushworth, 1957; Matthews, 1958). The present case was demonstrated to be an example of alpha rigidity in man. Henatsch and Ingvar (1956) demonstrated that large doses of intravenous chlorpromazine reduced the gamma rigidity of the classical decerebrate cat but had no effect on the alpha rigidity of the anaemically decerebrate cat. In man, chlorpromazine has no beneficial effect on the "gamma-rigidities" of Parkinsonsim and spasticity, and it was therefore most interesting to see some reduction of rigidity by intravenous chlorpromazine in our present case of alpha rigidity. There appears, therefore, to be a complete paradox in the actions of this drug in the cat and in man.

Intense muscular rigidity as a result of intrinsic damage to the spinal cord has been produced experimentally in cats by van Harreveld and Marmont (1939), Krogh (1950), and more recently by Gelfan and Tarlov (1959) in dogs. The latter workers temporarily occluded the high thoracic aorta for about 50 minutes, thus rendering the lumbo-sacral cord ischaemic. Severe rigidity of the hind limbs appeared as soon as the anaesthetic had worn off, and it resembled decerebrate rigidity in being most intense in the antigravity muscles. It differed, however, from decerebrate rigidity in being independent of the position or activity of the animal, and could only be abolished by anaesthesia. By analysing dorsal and ventral root potentials in response to nerve or root stimulation, they were able to show that the motoneurones lacked both inhibitory and excitatory internuncial activity and that the muscular rigidity depended largely on the continuous and spontaneous discharge of motoneurones. At necropsy, sections of the spinal cord showed destruction of the central gray matter of the cord, the anterior horns being relatively spared (Fig. 18). Our human case shows a very similar disorder of function to that described by Gelfan and Tarlov in their dogs. Reflex inhibition of

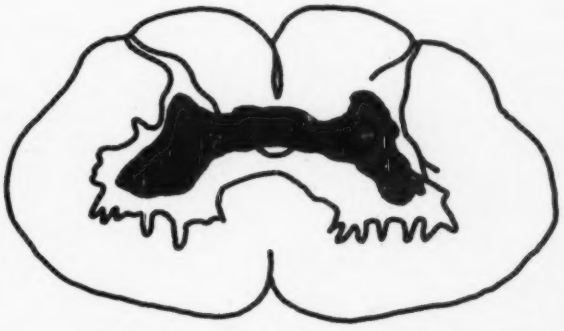

FIG. 18.—Drawing from Gelfan and Tarlov (1959) of the extent of the lesion in the lumbar cord in one of their experimental animals which during life had rigid hind limbs. (With the permission of the authors and of the editors of the *Journal of Physiology*.)

samples of surviving motoneurones such as those of the pectoralis major, the deltoid, and the triceps was absent, much reduced or even reversed, and excitation of these motoneurones either by muscle stretch by turning the head and neck, by noxious stimulation of the skin, or by volition, was small or absent. The motoneurones, therefore, were partially isolated from inhibitory and facilitatory connexions, yet the severe muscular rigidity was maintained by their constant firing and even spontaneously exacerbated.

Apart from the interplay of inhibitory and excitatory afferents on the motoneurone, a continuous discharge of the motoneurone is normally held in check by a self-induced inhibitory mechanism which employs special internuncial (Renshaw) cells (Renshaw, 1941). The motoneurones, by their axon collaterals, excite the Renshaw cells, which in turn inhibit motoneurones; the distribution of this inhibitory action is said to be non-specific and indiscriminate, and Eccles (1957) believes it can only serve as an "anticonvulsive" device. It has been suggested that strychnine and tetanus toxin block the Renshaw cell mechanism and the resulting muscular convulsions are due to the very high discharge rate of motoneurones released from this inhibitory control. The continuous muscular rigidity of our patient and the spontaneous spasms may have been due to interference with the Renshaw cell system, but very high rates of motoneurone discharge were not observed.

In the present case there are two separate features of the disordered physiology which need explaining: (1) The continuous and apparently spontaneous discharge of the motoneurones maintaining the rigidity; and (2) the inaccessibility of the motoneurone discharge to a number of reflex mechanisms and to volition. The latter constitutes a functional isolation of motoneurones; to correspond with this the histological sections show motoneurones surrounded by tumour cells and an extreme lack of ramifying nerve processes in the anterior horns.

It may be that motoneurones which are isolated from their nervous connexions but are otherwise normal will discharge spontaneously, as Gelfan and Tarlov (1959) suggested. These authors remind us that both denervated muscle fibres and denervated sympathetic ganglia discharge spontaneously, and they propose that "denervated" motoneurones behave similarly. However, the isolation of motoneurones might well produce changes in the cell which would result in spontaneous activity. In the present case, surviving motor nerve cells have a rounding off of their cell bodies and a lack of dendrites. The normal surface ratio is thereby reduced and this might conceivably result in spontaneous activity. Unfortunately, the pathological studies do not allow us to decide between the two hypotheses of the origin of the spontaneous activity, for the motoneurones were both isolated and had an abnormal morphology.

Summary

A patient with a cervical cord tumour developed intense, unremitting muscular rigidity of the arms, imposing on them a symmetrical posture similar to that of the decerebrate quadruped.

The rigidity was found electrophysiologically to be that of the "alpha" type. The motoneurones discharged spontaneously and were little influenced by reflex mechanisms or by voluntary effort.

The cervical cord contained an infiltrating malignant glioma, causing loss of nerve cells and fibres between C2 and C6.

The architecture of the anterior horns was disordered, leaving surviving motor cells of which the morphology was abnormal.

It is concluded that functional isolation of motoneurones can give rise to their spontaneous discharge and muscular rigidity.

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THE EFFECT OF THE REMOVAL OF THE NUCLEUS DENTATUS ON THE PARKINSONIAN SYNDROME

BY

SZABOLCS TÓTH

From the Institute of Neurosurgery, Budapest

Parkinsonism for long was dealt with only by neurologists and neuropathologists, but it became of great interest to neurosurgeons when the possibility arose that operation might solve the problem. Interventions were carried out on all those parts of the pyramidal and extrapyramidal system which could be considered on a pathological or experimental basis to be responsible for the development of the symptoms. Since the paper by Delmas-Marsalet and van Bogaert (1935) no account has been given of operations performed on the cerebellum. These authors found that after electrical coagulation of the dentate nucleus there was a slight diminution of rigidity whereas tremor became more marked. They stopped this intervention on account of complications arising in one of their patients, and as far as we know neither they nor others have since carried out operations of that kind. In the surgery of extrapyramidal diseases attention has been directed rather to interventions on the pallidothalamic system; and indeed some authors carrying out experimental research work considered that Parkinsonian tremor was of cerebellar origin (Carrea, Reissig, and Mettler, 1947, 1955). In their opinion Parkinsonian tremor is a result of a cerebellar lesion and further intervention on the cerebellum only increases it. However, according to Fulton (1949), after the isolated removal of the nucleus dentatus tremor (cerebellar intention) is of a transitory character and becomes only more marked after the removal of the nucleus globosus and emboliformis. We therefore decided to operate on the cerebellum in certain cases in order to diminish the Parkinsonian syndrome.

First, it seemed to us that hypotonia resulting from a cerebellar lesion caused by removal of the dentate nucleus might be expected to reduce rigidity but that no conclusions could be drawn from the published data concerning the question of tremor; either improvement or worsening of this symptom might follow the operation.

Secondly, it has become evident that surgical interventions on the pallido-thalamic system had not been so successful that we should not seek new operative methods to solve the problem. Again, among the successful operations on the thalamus there were some in the course of which the thalamic part of the dentato rubro-thalamic tract was disconnected. In these cases, tremor and rigidity diminished more markedly than after operations on the pallidum (Bravo and Cooper, 1959).

The possible disadvantages of causing a cerebellar syndrome had to be taken into consideration. We expected, however, that after the removal of one nucleus dentatus the disturbing side-effects would show a tendency to recover well. On the other hand, if we wanted to achieve prolonged results the efferent tracts of the cerebellum should be disconnected as extensively as possible in spite of possible prolonged side-effects. Also it was doubtful whether disconnecting the dentate nucleus in an intact extrapyramidal system would have the same effects as the operation in a pathologically defective one.

In two of our three patients we attempted a stereotactic operation on the pallido-thalamic system before interfering with the cerebellum. In one case we failed to carry out the procedure, and in the second case it did not prove very successful and the effects were not sufficiently lasting for it to seem worth while to repeat the operation.

Methods

After an incision along the midline and a suboccipital craniectomy we expose the vermis and medial parts of the hemispheres, and 3-4 mm. lateral to the midline an incision 2 cm. in length is made in the cortex parallel to the midline (Fig. 1). The white matter is removed together with the dentate nucleus by means of suction. We proceed sidewards, forwards, and backwards until the sulci appear in the sucker. We continue downwards till the lateral part of the fourth ventricle is opened (Figs. 2 and 3). By this means the dentate nucleus is almost totally removed. It is very important that the borders of the cavity should be distinguished after

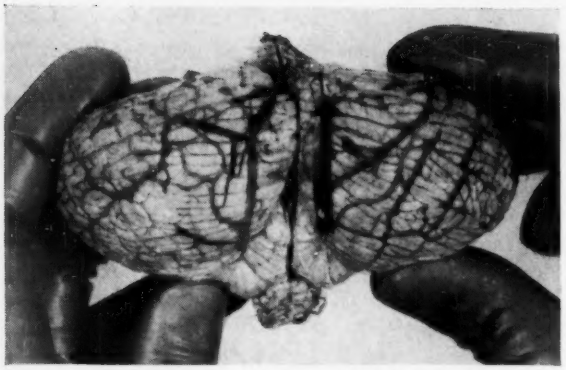

FIG. 1.—The arrow shows the line of incision.

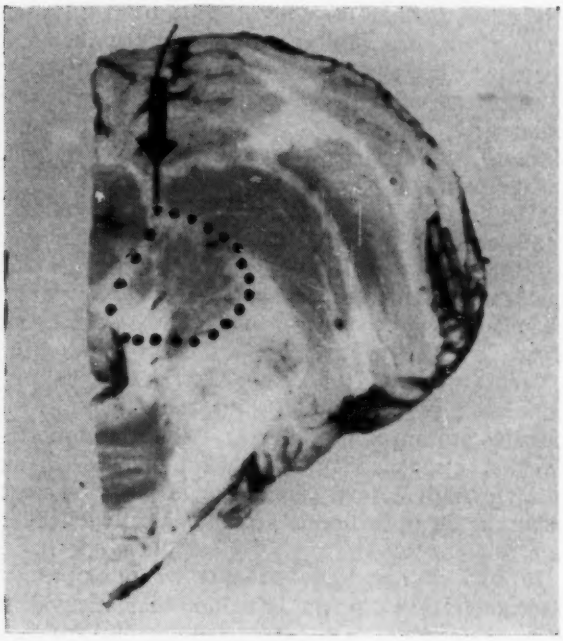

FIG. 2.—An arrow indicates the direction of penetration and a dotted line the part removed.

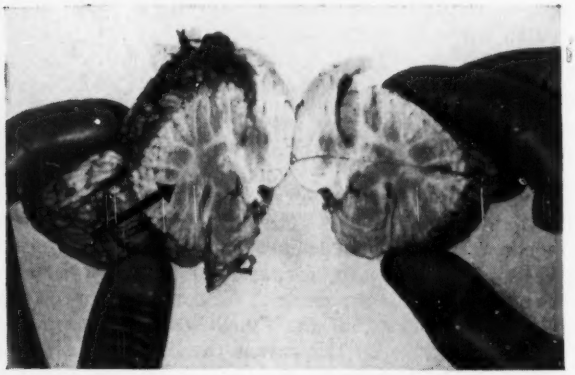

FIG. 3.—Sagittal section in the plane of the incision, an arrow indicating the direction of penetration.

removal of the white matter, for only in one of the cases was the structure of the dentate nucleus discernible (the first of our three cases). After the operation the cerebrospinal fluid empties from the fourth ventricle and if the veins of the sulci are treated carefully, bleeding is minimal. Tremor is registered by means of an electromyograph before and after the operation. In the course of the operation the dentate nucleus is stimulated at periods lasting 1-3 msec. at frequencies of 4 to 30 per sec. and 3 to 6 volts in amplitude (square impulse) and the changes of tremor activity in the upper extremity are registered.

Case Reports

Case 1.—A woman aged 56 years had had "Spanish flu" with high fever in 1930. She recovered without complaints or symptoms. Fifteen years later the extremities began to shake, posture became rigid, speech drawling, and gait slow. She had difficulties when eating and hypersalivation. Between 1950 and 1956 she was treated several times in neurological institutes, but only transitory improvement was achieved. The symptoms were more marked on the left side. On admission to our institute hypaesthesia of the left face and a reduced corneal reflex were observed on the left side. The left side of the body exhibited reduced sensation to pain and touch. There was considerable muscular rigidity all over the body and cog-wheel symptoms in the extremities. Bilateral tremor at rest was more marked on the left side. Gait was composed of small steps. Her speech was slurred and difficult to understand. She had a mask-like facies. Also her face was covered with a greasy secretion. There were reports of occasional oculogyral spasms. Electroencephalograms, radiographs of the skull and cerebrospinal fluid, ophthalmological, and otoneurological examinations did not show any remarkable abnormality. Slight diffuse dilatation of the ventricular system was found on lumbar pneumoencephalography.

Electromyograms taken before the operation registered the tremor on both sides, especially on the left where it was present at rest as well as during voluntary activity. The frequency of the tremor was 7-8 per sec., and its amplitude showed a marked increase during voluntary innervation, but the activity of the innervated muscle did not surpass that of other muscles and the tremor showed even at such times a marked antagonistic distribution.

As rigidity and hypokinesis were dominant among the symptoms, it seemed to be a case of the extrapyramidal syndrome suitable for approaching surgically by way of the cerebellum.

On January 15, 1958, the left dentate nucleus was removed. After the operation hypotonia on both extremities of the left side was detected; a few days later it increased. The patient exhibited no other cerebellar symptoms. The tremor on one side became less and the gradual improvement continued. Hypokinesis remained. The patient could perform fine movements more easily, but her skill at doing them did not show any appreciable change. Though the patient registered the improvement, she continued to complain about symptoms of hypokinetic origin.

According to the electromyogram taken after operation on February 7 the amplitude of tremor decreased approximately to half; the frequency did not change. During voluntary innervation tremor activity was less marked and the activity of the primary innervated muscle dominated. Almost two and a half years after the operation a control electromyogram was taken which showed further diminution of the tremor at rest to a tenth of its pre-operative activity. Frequency was 6 per sec. During voluntary innervation the activity of the primary innervated muscle was conspicuous. Clinical examination showed no rigidity. The patient's complaints and symptoms were chiefly derived from hypokinesis which could be controlled by drugs to some extent.

Examinations carried out after operation showed steady improvement regarding the rigidity and tremor, but for hypokinesis it showed periodical changes and thereby hindered the patient's movements.

Case 2.—S.M., a woman, aged 33 years, at the age of 6 had had a chronic disease with fever and disturbance of articulation and transitory abasia. At the age of 31, tremor of the fingers of the right hand began; pains in the right upper extremity and gradual weakening of the right extremities occurred. Tremor of the extremities increased to such a degree that the patient was unable to continue her work. In the course of the following years she was several times in hospital and received the most variable treatments, but no essential change occurred. On admission to our institute there was slight paresis of the right facial muscle and the tendon reflexes of the right side were enhanced, especially in the right hand. Moderate tremor at rest of the right upper extremity was observed, and from time to time rapidly increased in both extremities. Tremor fits occurred with variable frequency, but always as a result of excitement. Muscular hypertonia was not detected; the patient was unable to perform fine movements on the right side. Gait was rigid and spastic, though muscular hypertonia of the lower extremities was not observed. Imbecility was reported. The laboratory, radiological, ophthalmological, and otoneurological examinations showed no impairment of other systems. The patient, presumably as a consequence of an encephalitis hemisyndrome, had developed tremor at rest which was aggravated by action. As she showed no signs of improvement with drug treatment and was unable to work, we decided to perform stereotactic pallidothalamotomy. As repeated lumbar and cisternal pneumography failed to outline the ventricles, we dropped the idea of stereotactic operation, and the good results obtained by previously performed cerebellar operation encouraged us to remove the dentate nucleus of the affected side. Accordingly, on October 2, 1958, the dentate nucleus of the right side was removed. After operation the disturbance of movement completely ceased. Marked hypotonia of the right extremities was observed. Two or three days later intention uncertainty of the right upper extremity appeared and hypometria and ataxia of speech were found. Two weeks later intention uncertainty increased to intention tremor; later on tremor occurred also at rest. When the patient was made to leave her bed the disturbances of gait found before the operation disappeared. At first, on account of a strain to the right, the patient could walk only with support; a few days later the strain disappeared and her gait became perfectly undisturbed. Tremor of the right upper extremity remained unchanged or rather seemed somewhat increased. In January, 1959, the patient was sent for physiotherapy. Her tremor could be influenced to a certain extent by Artane. No tremor fits occurred after the operation. According to the electromyograms obtained before the operation, tremor at rest was about 300 microvolts in amplitude and 7 frequencies per sec. After the operation the amplitude of tremor was about 1,000 microvolts and the frequencies decreased to 5 per sec. The other symptoms, hypometria and ataxia of speech, improved.

On admission to our institute on June 18, 1960, the tendon reflexes were equal on both sides, tremor invariably more marked than before the operation, but the state of movement remained unchanged. Ataxia of speech had improved considerably, but was still perceptible; no disturbance of gait was recorded. Fits of tremor no longer occurred. With voluntary movement the tremor was distinctly diminished.

Case 3.—Dr. H.S., a man aged 52, could not give reliable information concerning former illnesses. The symptoms first began in 1951, when he noticed a slight tremor in the left upper extremity; as it increased, tremor occurred also in the left lower limb. Between 1954 and 1957 tremor extended to the right extremities. The patient's limbs became rigid as the tremor proceeded; he could hardly move and could not remain in a lying position for long because unbearable pain spread all over his body. On admission marked tremulousness of the tongue and lips was observed. There was tremor at rest of all extremities, more marked on the left side. The Achilles reflex on the left side was missing; otherwise no impairment of the reflexes could be detected. Muscular rigidity was universal, but was more severe on the left side. The patient could perform rough movements, but was unable to carry out fine movements. The attitude of the hands was of " *main d'accoucheur*". His posture was flexed and his gait rigid, composed of small steps. He had a mask-like face and his speech was quiet and slow. Rigidity diminished slightly after treatment with Artane, but responded in no other respect to any kind of drug treatment.

On account of a severe Parkinsonian syndrome, more marked on the left, and considering the fact that there was hardly any response to drug treatment, we decided to perform a stereotactic operation on the right side. On May 8, 1959, an electrolytic pallidothalamotomy was made on the right side (ansa lenticularis, the internal part of the pallidum in the ventrolateral nucleus of the thalamus). After pallidotomy rigidity decreased on the left; after thalomotomy tremor fits occurred and decreased perceptibly only a few days after the operation. Speech improved and the patient could better perform fine movements on the left side. About three months later gait improved, then gradually his condition worsened. Rigidity reappeared and became more marked on the right side. Electromyograms also proved the increase of

tremor, and clinical examinations, increased rigidity. In view of the fact that the effect of thalamopallidotomy was only temporary, and, in addition to the tremor, rigidity had also become prominent, we dropped the idea of a new sterotactic operation, but decided to remove the dentate nucleus of the right dise, where rigidity and tremor proved more severe. The operation was performed on March 17, 1960. During the operation the dentate nucleus was stimulated (3-6 v. amplitude, frequency 6 msec., periods 3 msec. square impulses), after two to three impulses tremor decreased on the right side, then it stopped. Using 3 v. this process was less definite, but still existed. After the operation marked hypotonia was observed in the right upper and lower extremities; the tremor ceased completely. Voluntary movements could be well performed but the "*main d' accoucheur*" attitude of the hands and hypokinesia remained, in spite of the fact that fine voluntary movements, if only to a small degree, could be performed. In a week or so, hypertonia appeared occasionally in some muscles, but this remained transient and ceased after a few passive movements. About a week later slow undulating movements could be observed in the right extremities at rest. According to the control electromyograms the occasional movements corresponded to 3 per sec. tremor activity. The frequency of tremor before the operation was 6 per sec. There was a marked difference between the amplitude of tremor activity before and after operation. After the operation tremor activity during voluntary movement became unstable and for most of the time was not distinguishable in the normal interference pattern.

Control examinations carried out on June 17, 1960, showed hypotonia of the right upper and lower limbs invariably and especially marked in comparison with the left extremities. There were long tremor-free periods of the extremities, especially in the upper limb, followed by periods of tremor. Nevertheless, during these periods tremor was also less marked on the right side than on the left. The difference of frequencies remained unchanged.

Discussion

Hypotonia is a fundamental constituent of the neocerebellar syndrome. It is most marked in the human and progressively less noticeable as we proceed backwards in phylogenesis. It was the most prominent symptom after operation in our patients, appearing in each of our cases. It was permanent. It was more marked than after our pallido-thalamic operations, especially in our third patient, whose rigidity could with difficulty be overcome by passive movement. Improvement set in immediately after the operation and not only was the normal tone achieved but hypotonia developed. Therefore it appears that the tone-regulating function of the neocerebellum has the same tendency in Parkinsonian disease as in the intact system. At the same time hypotonia must be considered as a real deficiency symptom of the cerebellum, because it appears immediately after the operation, it remains after the shock period, and it remains unchanged at the beginning of the period of compensation and later shows only gradually a slight decrease.

Sherrington (1898) proved that stimulation of the anterior cerebellar lobe decreases decerebrate rigidity and its removal increases it. Similar results were obtained with anaemic decerebrate preparations of Pollock and Davis (1927), where ischaemia of the anterior cerebellar lobe increased further the decerebrate rigidity (Stella, 1944; Granit, Holmgren, and Merton, 1955). These cases, however, do not contradict each other because Parkinsonian rigidity is not the same as decerebrate rigidity (von Kiss and Fényes, 1934; Mettler, 1957). In our cases the intention was to eliminate the neocerebellum (nucleus dentatus), while in decerebrate experiments it is the anterior cerebellar lobe which is disconnected. It is important to note that after the removal of the dentate nucleus the spastic gait of our second patient ceased and this effect proved to be prolonged.

Regarding tremor, in two of our patients (Cases 1 and 3), especially in Case 3, there was a marked diminution after removal of the dentate nucleus. This decrease became even more marked two and a half years later in the case of our first patient. In the second patient the amplitude of tremor increased considerably, but in both the second and the third case the frequency of tremor was markedly decreased.

Clinically, the tremors occur in two forms which are easy to distinguish from each other. In the first case the tremor is more marked when the patient is at rest and during action it ceases or decreases. In the second case, at rest, there is no tremor activity and it occurs and increases during action. The first is the Parkinsonian and the second the cerebellar type of tremor. Undoubtedly, these two tremors are distinguishable in their appearance, but electromyographic examinations do not separate the two types of tremor from each other. The distinction is made possible by other symptoms of the syndrome. This uncertainty exists not only in the distinction of clinical symptoms, but also regarding the site of origin and character of tremor connected with it. Mettler and his collaborators (1957) observed that after the removal of the nucleus dentatus or after the lesion of the brachium conjunctivum true Parkinsonian tremor (at rest) appears, and in their opinion Parkinsonian tremor is probably of this origin. Delmas-Marsalet and van Bogaert's unparalleled operations tend to justify this theory, for on coagulating the nucleus dentatus they found that the Parkinsonian tremor was increased.

Peterson, Magoun, McCulloch, and Lindsley (1949) considered the brain-stem reticular substance to be responsible for the occurrence of tremors, and Alexander, Székely, and Spiegel (1959) observed that

stimulating the nucleus dentatus increased the tremor originating from the brain-stem lesions; from this it follows that the removal of the nucleus dentatus should diminish or abolish the tremor. Cooper's operations on the thalamus support the theory that the absence of cerebellar influence decreases the tremor. Wycis, Székely, and Spiegel (1957) in another series of experiments found that on cutting through the brachium conjunctivum tremor could be produced by stimulating the reticular substance of the brain-stem. It is evident that the occurrence of tremor is a combined phenomenon. It must depend on the failure of a system not quite understood which may cause tremor, while a lesion of this system may lead to the decrease of tremor. According to Walshe (1927) and Demole (1927), cerebellar tremor is the result of insufficient cortical cerebral compensation. According to Aring and Fulton (1936), only complete removal of the motor area can decrease cerebellar tremor while its partial removal rather increases it. On the basis of the findings of Bucy and Case (1937) and of Walker (1955) it is known that the injury of the motor cortex and of the corticospinal tract diminished Parkinsonian tremor, a diminution proportional to the grade of lesion of the motor cortex. In this respect our second case is of interest. This patient showed the most marked signs of a cortical lesion and after removal of the nucleus dentatus tremor markedly increased. After the operation the tremor was first of a cerebellar type but changed gradually to the typical Parkinsonian tremor. Experimental examinations show that the site of the lesion does not determine the character of the tremor. The above case shows that if tremor already exists, the lesion of another potentially tremor-causing site does not necessarily change its character.

It is interesting to note that in the case of our two patients, besides the marked hypotonia, there were no other cerebellar symptoms; in the third case, at the most there was slight hypometria. As for the second patient, the cerebellar symptoms began to develop only on the third and fourth day, suggesting that in the development of cerebellar symptoms the compensatory mechanism plays an important role. Inability to perform fine movements cannot be estimated as a cerebellar symptom, because such impairment existed also before the operation and there was if anything a slight improvement after the cerebellar operation.

Our cases confirm the opinion that the rigidity, hypokinesis, and tremor are not strictly connected with one another because when rigidity markedly decreases, hypokinesis does not show substantial improvement, and in two cases decrease of rigidity was not followed by increase but by decrease of the tremor.

Summary

The nucleus dentatus on one side was removed in three cases of the Parkinsonian syndrome. In all three cases a marked decrease of tone and considerable diminution of rigidity was observed. Tremor was markedly decreased in two cases and increased in one. When tremor and rigidity were diminished, the results were prolonged. Other Parkinsonian symptoms were not substantially influenced by surgical interventions on the cerebellum. After removal of the nucleus dentatus hypotonia is the only genuine cerebellar deficiency symptom which appears.

From a study of these cases it seems that rigidity, tremor, and hypokinesis are phenomena of comparatively independent existence varying independently of each other.

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SOME EXPERIMENTAL OBSERVATIONS ON THE ACTION OF INTRAVENOUS HYPERTONIC UREA IN DOGS, WITH PARTICULAR REFERENCE TO PLASMA VOLUME AND TISSUE UREA CHANGES

BY

SHEDDEN ALEXANDER, J. C. EATON and H. J. FREEDMAN

From the Royal Infirmary, Glasgow

Several publications in recent years by Javid and his colleagues have reported on the use of hypertonic urea solutions to reduce the brain bulk in intracranial operations and to lower intracranial and intraocular tension (Javid, 1958a and b, 1959). That urea is a primary diuretic substance has long been known, but that the effect of hypertonic urea is not due to this diuretic action has been shown on nephrectomized monkeys (Javid and Anderson, 1959b). It has also been shown that the plasma electrolyte levels do not change appreciably (Garvin, Jennings, and Gesler, 1959).

Two explanations have been put forward to account for the shrinking action of urea on brain tissue. (1) A blood cerebrospinal fluid barrier is implicated by Javid and his colleagues: "The prolonged fall in cerebrospinal fluid pressure in nephrectomized monkeys is due to a prolonged osmotic pressure differential between blood and cerebrospinal fluid". (2) A blood-brain barrier, as originally postulated to exist by Weed and McKibben (1919), is implicated by Stubbs and Pennybacker (1960): "The reduction in brain bulk is obviously much greater than that of other soft tissues and we think that a barrier to the entry of urea into brain best explains our clinical observations".

The withdrawal of water from brain and cerebrospinal fluid must produce an increase in volume in some other compartment of the interstitial space and most writers acknowledge that the plasma volume rises and a state of hypervolaemia is induced (Tench, Javid, and Gilboe, 1960). We have not, however, encountered an assessment of this increase in plasma volume, and a neurosurgical case indicated that there was a very large increase in plasma volume. Estimations of plasma volume by the dye dilution technique in an average-sized adult patient who was given hypertonic urea before a neurosurgical operation revealed an increase in plasma volume of the order of 2 litres. This was far greater than could be accounted for even had all the water been removed from brain and cerebrospinal fluid and prompted us to question the blood-brain barrier explanation. To elucidate the point a small series of experiments in dogs was performed with hypertonic urea infusions and the results are presented.

Material and Method

The plasma volume of three dogs was estimated by measuring the dilution of Evans blue dye. Urevert (30% urea in 10% invert sugar) was infused intravenously, 1·5 g./kg. dog (Javid and Anderson, 1959a). Blood, muscle, and brain samples were taken before, and at five, 10, and 15 minutes after infusion of the Urevert, up to 55 minutes, and urea, nitrogen, and water content determined. Muscle and brain urea were determined by homogenising the tissue, after weighing with a measured volume of water, centrifuging it, and measuring the urea content of the supernatant tissue fluid. Urine urea and urine flow rate were determined on samples from an indwelling urethral catheter. The femoral artery and vein were cannulated and blood pressure changes observed manometrically.

Results

The results are shown graphically in Fig. 1, where the rise in plasma volume is expressed as a percentage of the initial volume. The absolute values for plasma volume are given in Table I. The rapid, initial rise in plasma urea and its subsequent rate of fall is paralleled by the rapid initial rise in plasma volume and its subsequent fall.

TABLE I

ABSOLUTE INCREASES IN PLASMA VOLUME

	Dog No. 3 (22 kg.)	Dog No. 4 (18 kg.)	Dog. No 5 (23 kg.)
Initial plasma volume (ml.)	1,730	725	1,168
Maximum increase in plasma volume after urea (ml.)	910	155	548

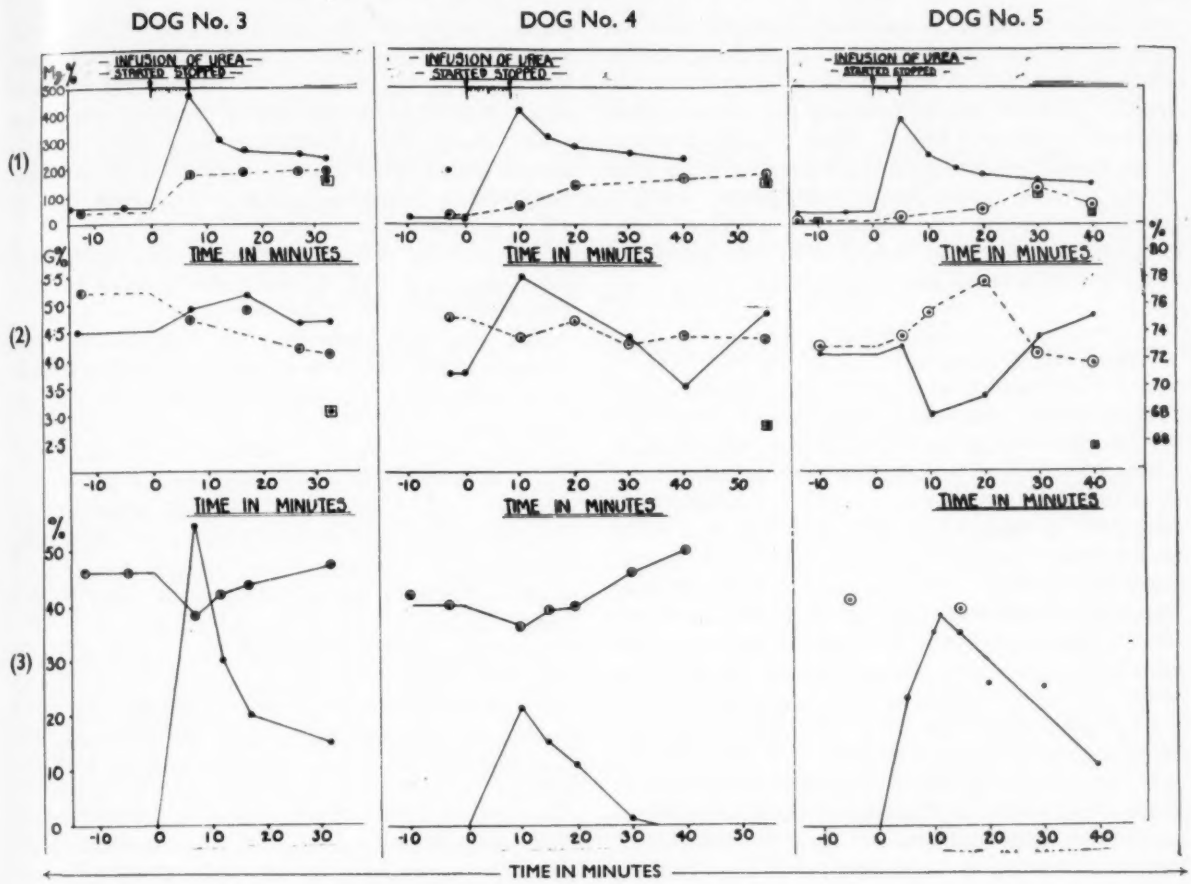

FIG. 1.—Graphs to show changes in plasma urea, plasma volume, haematocrit, muscle urea, brain urea, muscle nitrogen, and muscle water.

Key to graphs (1) Plasma urea; Muscle urea; Brain urea
(2) Muscle water; Muscle nitrogen; Brain nitrogen
(3) Increase in plasma volume as %; Haematocrit

	Dog No. 3 (weight 22 kg.)		Dog No. 4 (weight 18 kg.)		Dog No. 5 (weight 23 kg.)	
	Before Urea	After Urea	Before Urea	After Urea	Before Urea	After Urea
Urine flow rate (ml./hr.)	37	187	—	—	259	75
Urine urea (g. %)	3·65	2·98	—	2·35	2·6	3·26

The haematocrit curve has been inserted since there was a considerable discrepancy in the rise in plasma volume calculated from the haematocrit, and the absolute rise determined by the Evans blue method, being much greater in the latter. The muscle urea will be seen to rise as the plasma urea falls, indicating that urea is entering muscle from plasma fairly quickly. In the first two dogs brain was sampled only at the end of the experiment, but it can be seen from brain urea levels that urea was also entering brain from plasma fairly quickly. The curves for muscle water and muscle nitrogen are best interpreted in conjunction with the curve for muscle urea. In dogs 3 and 5, as muscle urea rose, water rose and nitrogen fell. In dog 4 the relationship is less clearly seen.

The infusion in dog 3 produced a considerable diuresis. In dog 4 trouble with the catheter prevented full determinations, although the low urea concentration of the urine sample at the end of the experiment suggested that a diuresis had taken place. In dog 5 there was a very pronounced reduction in the flow of urine, the urine urea rose, and laparotomy at the conclusion of the experiment confirmed that the bladder was empty.

The lack of any continuous recording of arterial and venous pressures proved to be a disappointing omission where the time factor counted in such

very short intervals. It was clear, however, that the central venous pressure rose immediately after infusion then fell to the initial level and that the arterial pressure dropped during this period, then returned to pre-urea levels. These changes conform to the known pattern of blood pressure changes after infusion of a concentrated electrolyte solution (Evans, 1930) but the failure to correlate them accurately in time with the other changes precludes any conclusion being based upon them.

Discussion

The absolute increase in plasma volume was of such a magnitude as to suggest a general withdrawal of fluid from body tissues. The figures for plasma urea, muscle urea, muscle nitrogen, and muscle water showed that water was leaving muscle and entering plasma so long as urea was more concentrated in plasma than in muscle and that when urea began to enter muscle in appreciable amounts water returned to muscle. It was apparent that urea was also entering brain at much the same rate and to the same degree as it was entering muscle, and that presumably a generalized blood-tissue osmotic gradient obtained. The deceptively large reduction in brain bulk seen when urea is infused in neurosurgical cases we would put down to the peculiar situation of brain in a rigid bone framework. These experiments lead us to discount the importance of a blood-brain barrier after the infusion of hypertonic urea and to postulate that a generalized blood-tissue osmotic gradient prevails.

In future experiments it is hoped to show to what extent changes occur in the volume of interstitial fluid and in plasma osmotic pressure. In these calculations the volume of solutes was neglected and in future it would be better to express the changes in water in the fluid compartments in terms of true water. The figure really required is the volume of plasma water not of plasma. A rise in blood urea of 327 mg. % represents a rise of 54·5 mOsm. The normal osmolar value for mammalian plasma being of the order of 289 mOsm., this represents a rise of 18·9%. Except in one dog when it was 20%, the increase in plasma volume was much greater than this which suggests that when water enters the extracellular fluid from cells it carries with it other solutes, presumably to maintain equilibrium between normal constituents in cell water and extracellular fluid.

The striking reduction in urine flow after urea infusion in one dog is attributed to renal haemodynamic factors peculiar to the dog.

The disparity between the haematocrit and absolute plasma volume is attributed to the release of red cells into the circulation from depots such as the spleen.

Summary and Conclusions

Three dogs were infused with hypertonic urea solution (Urevert). Determinations of water and urea changes in plasma, muscle, and brain were made. ("Water" in this context is used rather loosely as pointed out in the discussion.)

It is concluded that Urevert has a powerful and transitory effect in increasing plasma volume, and that this effect is caused by the production of a generalized blood tissue osmotic gradient and the consequent removal of water equally from different tissues.

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ON THE COEXISTENCE OF EPILEPTIC SEIZURES AND ABNORMAL INVOLUNTARY MOVEMENTS*

BY

JERZY CHOROBSKI and TADEUSZ BACIA

From the Department of Neurosurgery, Academy of Medicine, Warsaw, Poland

Merely to nerve oneself to dare to speak on even a few of the many aspects of epilepsy and its allied pathological conditions is a brave venture, but to face such an assembly as this might surely be considered a sign of overconfidence. However, we, the pupils of the men taught by Charles E. Brown-Sequard, John Hughlings Jackson, William Gowers, and other neurologists of a similar calibre, feel it our duty to try to hobble along the path they walked so masterfully, and to present for analysis and judgment the fruits of our own modest endeavours.

This is indeed an appropriate time, as we are celebrating the centenary of "Queen Square", the Mecca of all neurologists, and the place of work of John Hughlings Jackson (1835-1911), undoubtedly the originator of much of our contemporary neurological thought on the epilepsies in particular. He had, as is well known, extraordinary foresight, for his many hypotheses have been fully verified by modern means of investigation.

Our contribution to Jackson's masterpiece on the problem of epilepsy is based on some six clinical observations. These raise questions which we should like you to help us to answer. The important question is: Are the abnormal involuntary movements, be they tremor or some choreo-athetoid movement, on the one hand, and, on the other, epileptic seizures, both of which occur in the same individual, caused by a single pathogenic focus, or are these two abnormal motor phenomena produced by two lesions separately located?

One aim of this communication is to summarize briefly three of six case histories and to present the relevant E.E.G. and E.C.G. findings, so that you may analyse them and draw from them some possible conclusions. However, it is not very surprising that we feel unable to refrain from trying to answer the question ourselves. In order that our answer, presented here in the form of a hypothesis, may seem to be based on a firm foundation it is necessary to give a brief account of some of the ideas on the subject previously held by other investigators.

There is indeed "nothing new under the sun", for the above questions were posed in one form or another in many of Jackson's works on epilepsy, but we believe that they were not clearly answered. We remember, of course, that he considered the "epilepsies" to be a paroxysm dependent on a sudden temporary excessive discharge from some highly unstable region of the cerebral cortex. There is, in other words, if we follow Jackson aright, in each variety of epilepsy a "discharging lesion of some region of the cerebral cortex", and this is "nothing more than a group of cells whose instability is raised far above normal".

The same may be said about another variety of, to use Jackson's nomenclature, the "hyperkineses", namely, chorea, for he writes "my investigations lead me to the 'inevitable' inference that the movements observed in chorea depend on unduly high instability of nerve cells". Although he speculated "that, anatomically, the lesion responsible for chorea was to be usually found in some convolutions of the motor area", he was ready to admit in 1868 that neither the site of the lesion (such as plugging of arterioles) nor the pathological process leading to it were known. He stated that on the anatomy and pathology of chorea all of us have hypotheses only. Discussing the patho-physiology, he said that it was clear to him that the cells and fibres governing the muscles so "copiously" moving, as in chorea, cannot be grossly destroyed. On the other hand, "since the movements of these muscles are disorderly in association, and in succession, the nerve cells and fibres cannot be healthy. Therefore, wherever in chorea the lesion may be, and whatever may be its particular cause, it is clear that its abstract nature (that is, detached from the incidents of any particular case, to use, this time, Herbert Spencer's terminology) must be one betwixt loss of

*A paper read at the centenary celebrations of the National Hospital, Queen Square London for Nervous Diseases in June, 1960.

function leading to paralysis of motion, and healthy function allowing the orderly movements of health. "In short, nerve-tissue in chorea as well as in other varieties of hyperkineses is neither destroyed nor healthy—it is irritable." Jackson considered, therefore, chorea and convulsions to be movements resulting from discharges of the cerebral cortex. The literature on the coexistence of these syndromes, in which the chief manifestations are abnormal involuntary motor acts, be they in the form of epileptic seizures or choreo-athetosis, is large and its proper analysis is out of the question in the short time at our disposal. Let us, however, note that Russell in 1899 found, on examining some 5,000 case histories, an extraordinarily frequent coexistence of epilepsy and chorea. Hartmann and di Gaspero (1914) maintained the same in their article on epilepsy in Lewandowsky's *Handbuch der Neurologie*, published in 1914. This combination was noted by Foerster in 1921 and 1926, and he mentioned this opinion held in Bechterev's (cited by Foerster, 1926) Féré's (1890), Binswanger's (cited by Foerster, 1926), and Lewandowsky's (1914) works. In 1904 Foerster published his own observations on paroxysms of choreiform movements occurring both before and after epileptic seizures or as epileptic equivalents. According to him, they were "undoubtedly" caused by a lesion of a like nature. Yet, he added, that since the pathological changes observed in such cases, for instance by Stertz in 1921, were mainly located in the corpus striatum, the lesions responsible for the epileptic seizures must be looked for elsewhere than in the basal ganglia. As the epileptic fits cannot be of "striatal origin" it must be inferred that the two sets of involuntary movements result from two separate lesions.

One recalls that in the years following the great epidemics of lethargic encephalitis Parkinsonism was common. There were also many clinical reports describing seemingly new types of fits, such as "extra-pyramidal" by Sterling in 1924 and by Wimmer in 1925, "striatal" or "subcortical" by Spiller in 1927, and "spastic" by Knapp in 1919. Wilson in 1940 pointed out that this conception was no novelty, except the names, because cases of that kind had long been known to Collier (1928) and to Wilson himself. The discovery, as pointed out by the last author, of striatal lesions post-mortem by Stertz (1921) is, of course, no proof of the striatal origin of the fits. On the contrary, they most probably had an extrastriatal source, since these ganglia were the seat of destructive processes.

Here, we must add a few words about the far from rare combination of myoclonus with epilepsy, known as Unverricht-Lundborg's myoclonic epilepsy. The Lundborg (1912) type asserts itself as a myoclonic aura of a major epileptic seizure, or as its motor equivalent. The so-called second type of this syndrome, the continuous myoclonus of Kojewnikow, seems to be a sequel of a local inflammatory process. It is interesting to note that extirpation of the cortex involved abolishes the local hyperkinesis, as reported by Grinker in 1937. The third type, progressive familial myoclonus of Unverricht (1891), begins with a generalized attack; it is only rarely that myoclonic jerkings occur at the start of the disease. Unfortunately, nothing is known about the patho-physiology of this most interesting syndrome, so we end this paragraph by quoting Wilson, who in 1940 said that it "does not differ in any essential feature from the clinical commonplace of fits combined with jerks".

Now, returning to the problem of strict localization of this or that type of epilepsy, let us recall that though Jackson used the term striatal epilepsy, he also used such phrases as "unilateral convulsion", "hemiplegic epilepsy" or "convulsions beginning unilaterally". But is it not true, as has been so well expressed in 1953 by William G. Lennox, one of the most eminent contemporary students of epilepsy, that Jackson's greatest achievement is not his description of a certain seizure pattern but his formulation of concepts or principles that explain seizures of all sorts.

What interested Jackson was the study of the "morbid alteration of the normal function of nerve tissue" and the need to understand the functioning of the brain in health. Jackson asks what is the function of the healthy nervous system. It is to store up and expend force. It is the function of nerve units, in expending their stored up force, to develop certain more or less complex movements, in correspondence with special, not always constant, excitations which bring the local movements into harmony with the whole organism. And finally there are, for him, two kinds of alterations of function due to disease: loss of function and over-function. In the latter, more nerve force is stored up than in health and more is therefore expended; the nerve tissue is highly unstable. Under the first heading come palsies, akineses, anaesthesiae; under the second chorea, the epilepsies, tetanus, the hyperkineses, neuralgia, etc. In a footnote he added to the above-quoted words a very significant remark, namely, that "the functional change of nerve tissue in epilepsies, in chorea and in tetanus, is supposed to be the same".

All this is not only of great interest for anybody studying the history of Jackson's neurological ideas, but of very special value to our own approach to the problem of the pathomechanism of the hyperkineses. We will shortly show why this is so, but first let us give a very brief account of our own observations.

We have had under our observation six patients in whom epileptic seizures were concomitant with choreo-athetoid or simply athetoid movements. Two of them have been operated upon, and in another the brain has been examined by means of ventriculography. In these three patients we were able to demonstrate that those two syndromes may be caused apparently by two differently located lesions. The one responsible for abnormal involuntary movements is probably of a special, most often, diffuse nature. This had been proven to our satisfaction by the facts, first that the excision of the motor cortex, made in order to relieve the patient of his choreo-athetoid movements, actually brought about cessation of these movements while the epileptic seizures continued, and secondly that not until the pertinent epileptogenic focus, localized by means of E.E.G., E.C.G., and by electrical stimulation in another region of the brain than the motor cortex, had been removed did the epileptic fits cease.

The excision of a relevant area of the motor cortex, a procedure used by Horsley (1909) and Bucy (1942) in cases of abnormal involuntary movements of all kinds, is a palliative operation. The rationale for its use is that by attacking a strategic point in the pyramidal and extrapyramidal nervous systems it is possible to interrupt a vicious circle of pathological nervous impulses causing these abnormal movements. We will return to this later.

Obviously, when the epileptogenic focus happens to be located in or around the motor cortex itself, then the excision of that cortex is followed by cessation of both the epileptic seizures and the choreo-athetoid movements. This has been observed in the second of our patients. We may consider, therefore, the results in this second patient most important in our study of the problem, especially when we compare the results with those obtained in the first patient.

The case histories of these two patients will be given in some detail, as well as that of a third patient. This last case has been added because it presented an exceptionally interesting phenomenon, namely, complete cessation first of the athetoid movements, then of the epileptic seizures, both following a simple ventriculography.

Case Reports

Case 1.—B.T., a girl, aged 15 years, when 3 years old, suffered severely from whooping-cough, during which she started to have generalized epileptic fits, with a visceral aura, loss of consciousness, and clonic movements of the right hand. At first the fits occurred three times a year, and recently several times a week. The reason for her admission was a severe status epilepticus. After the first epileptic attack the child lost her speech and became paralysed down the right side. Recovery took place to some extent, but her right hand, weak and spastic, became the seat of typical athetoid movements. The girl was neuropathic and mentally retarded. Ventriculography showed only a dilatation of the left lateral ventricle including the temporal horn. The E.E.G. tracings, taken before her first operation, indicated that we were dealing here with two aspects of abnormal electrical activity. First there were episodes of spikes and slow waves located in both temporal lobes, and secondly diminished voltage, suggesting diffuse cerebral damage.

After having ascertained at operation the exact position of area 4, especially that part controlling movements of the upper extremity, we sucked out that portion subpially on April 18, 1958. We did not touch the temporal lobe, which was macroscopically apparently normal. In the electrocorticogram, however, prominent spikes and slow wave complexes were picked up from over the temporal lobe. As expected the athetoid movements ceased, but improvement lasted only for some three months, when some abnormal movements returned. She continued throughout to have epileptic seizures, and the E.E.G. examination confirmed the presence in the left temporal lobe of a focus of frequent spikes and slow waves. It is true that the spikes were now less frequent than before the operation and were of lower voltage, but they still were there.

She was, therefore, operated upon for the second time on November 4, 1958. Because electrical stimulation of the cortex, close to the previously sucked-out area, was yielding definite movements of the right fingers and the hand and she still had some athetoid jerks, it seemed that we had not removed sufficient of area 4 for her hand movements. We therefore sucked out more cortex from area 4. It was our hope that not only would we relieve the patient of the athetoid movements completely, but that perhaps this added excision of the motor cortex would also influence the epileptic seizures. As the E.E.G. and electrocorticogram from over the left temporal lobe was less abnormal than previously, the lobe was not excised. After this operation the athetoid movements ceased completely but the epileptic fits continued to torment the patient.

We submitted her, therefore, one year later, on December 18, 1959, to a third operation, during which we produced by electrical stimulation of the upper temporal region her typical epileptic seizure, thus confirming the presence of an epileptogenic focus, which was only assumed from the E.E.G. and E.C.G. tracings. Consequently, we sucked out this area. Our hopes for improvement were fulfilled, for the patient finally became free of the epileptic fits. The E.E.G. from over the excised temporal area showed no spikes and slow wave complexes. It is true that only six months have elapsed since the last operation, but the patient continues to be well. We must add that before the operation full medical anticonvulsant treatment had been of no avail.

Following presumably an acute virus encephalitis at the age of 3, the girl, after a short period of complete loss of speech and right-sided spastic

paralysis, developed generalized epileptic seizures, starting in the right hand, and also athetoid movements of the right hand and fingers. Removal of the relevant motor cortex relieved the patient of the athetoid movements, whereas the epileptic fits only ceased after excision of the epileptogenic focus, which was located, by means of E.E.G. and E.C.G. tracings and electrical stimulation, in the left temporal lobe. Later E.E.G. examination showed, however, that the slight but diffuse abnormal electrical activity was not confined to the temporal lobe, but was evident over both sides of the brain, presumably being the result of diffuse damage by the whooping-cough infection.

We believe, and will try to explain more fully later on, the reasons for our belief that the pathomechanism of this patient's athetoid movements is to be looked for in a disturbance in the dynamics of the nervous pathways, the integrity of which is necessary for the performance of any normal motor act. We believe that this disturbance was caused by the diffuse damage to the brain. The epileptic seizures, on the other hand, must have been produced by a lesion, located in the temporal lobe. What the nature of this lesion may be, we do not know.

Case 2.—M.W., a girl, aged 11 years, without any apparent cause, had developed, at the age of 11 months, left-sided epileptic seizures, starting in the left hand. After this, she developed a spastic hemiplegia, and choreo-athetoid movements in the left hand and fingers. To these left-sided epileptic fits beginning unilaterally and occurring once or twice a month, there were added, at the age of 4 years, peculiar attacks about once a month, characterized by a laryngeal and oesophageal spasm, reddening of the face, a loud shriek, jerking of the left extremities, without loss of consciousness.

Electroencephalographic tracings, typical for all cases of that or the other type of abnormal involuntary movement, favoured a diffuse pathology. There were present so-called slow spikes. An electrocorticogram done at operation on March 5, 1958, showed an area of abnormality more evident over the right motor gyrus, close to the first temporal convolution. It was characterized by sharp waves, and two or three episodes of apposition of waves at nearby electrodes. This area corresponded to a spot in the precentral motor gyrus, the white matter of which was definitely tough and the leptomeninges covering it were whitish and thick. Electrical stimulation of this region proved it to be precisely the motor area for hand and finger movements. By slightly increasing the usually employed parameters of stimulation, we produced her typical epileptic seizure, *i.e.*, one starting with flexion of the left hand and fingers. From no other region of the exposed cortex, not even from that in the closest vicinity of the recently stimulated area, and not even with strongest stimulation, were we able to produce a fit. Presumably this was an epileptogenic focus, and since this region corresponded exactly to area 4 for hand movements, we performed the Horsley-Bucy operation. This was carried out on March 5, 1958, and as expected from our previous experience of some 50 cases using the same procedure, we immediately and completely relieved the child of the choreo-athetoid movements. The relief remained even after recovery from the transient hemiplegia. The epileptic seizures continued for some eight months, in spite of continuous and heavy anticonvulsant treatment. An E.E.G. examination, made after pentothal provocation, demonstrated in the left temporal lobe a definite pathogenic focus which had not been seen in the straight E.E.G. (Fig. 1). Then, though there was no change in treatment, the epileptic fits ceased, and have not reappeared during the 18 months in which the patient has been followed up.

This is, it seems to us, an important case. The epileptogenic focus was placed more or less exactly in the motor area for hand movements, which was macroscopically grossly abnormal. Its excision, done to relieve the patient of her abnormal involuntary movements, freed her, therefore, both from the epileptic seizures and the choreo-athetoid movements. We have all been taught that a patient suffering from epileptic fits loses them the moment he becomes paralysed. We know, however, that this is not always true, and should the epileptogenic focus be localized elsewhere than in or about the motor region, than even a complete and long-lasting paralysis, caused by the excision of the motor cortex, does not necessarily mean cessation of epileptic seizures.

Case 3.—S.S., a man, aged 23 years, some six months after a head injury, followed by unconsciousness for two weeks, began to have epileptic seizures, ushered in by an aura lasting for about half an hour, during which time he felt suddenly weak and generally "bad", and had troublesome vertigo. The tonic-clonic, generalized fits, of which he had had three in the seven months before his admission began with loss of consciousness, rotation of the head and body to the right, and jerking of the right hand This was followed by a temporary paresis. The E E.G. showed a slight bilateral and diffuse abnormality without any characteristic details (Fig. 2). Since there was a history of a head injury and a purulent discharge, particularly from the right ear, ventriculography was done on October 13, 1958, to exclude an abscess. No abscess was found. It was most interesting that some 11 days after ventriculography the athetoid movements of his right hand, which had appeared some time after the injury, disappeared completely. There was also some slight improvement in the E.E.G., though the tracings were by no means normal.

It is true that during the patient's three-week stay in hospital we never observed an epileptic seizure, but this seems to us of little signficance as he had had them so rarely anyway. However, the disappearance of the abnormal involuntary movements

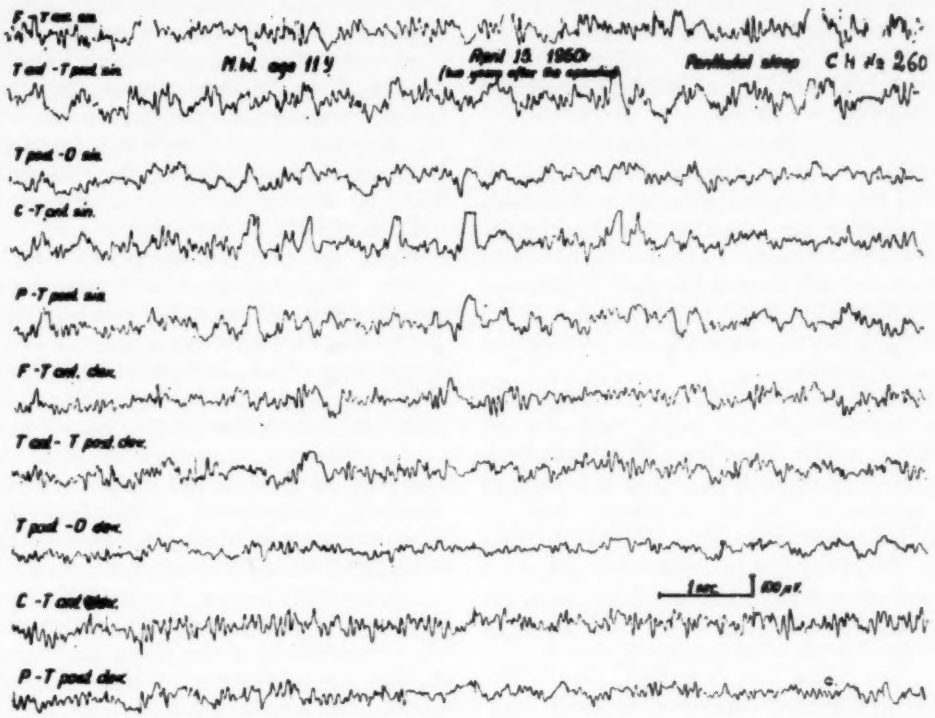

FIG. 1.—E.E.G. tracing (Case 2) demonstrates in the left temporal lobe a definite pathogenic focus not seen in the straight E.E.G.

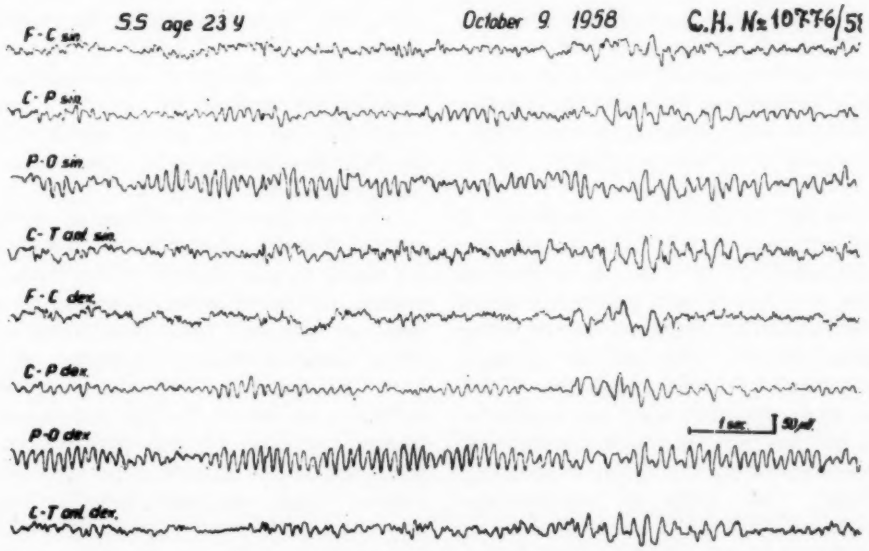

FIG. 2.—E.E.G. tracing (Case 3) shows a slight bilateral and diffuse abnormality without any characteristic details. This is an E.E.G. picture typical in cases of abnormal involuntary movements.

is, at least, interesting though not entirely unexpected. We have observed them go, when caused by a brain tumour, after simply opening the dura mater. The implication of this certainly unusual phenomenon needs some comment later.

Allow us to add the following few words about the rest of our cases. As already mentioned, the E.E.G. and the E.C.G. tracings were in all of them abnormal. One of our tracings demonstrated this abnormality which is as a rule asymmetrical. In the CT right anterior tracing we see there a complete absence of the alpha rhythm, with some episodes of fast waves of relatively high voltage while on the left side the alpha waves are present.

Sometimes, no signs characteristic of epilepsy are to be found in the E.E.G., as in the case of a girl aged 13 years. On the other hand, there usually is some asymmetry in the tracings, pointing towards the site of, as it were, "epileptic readiness", and not to the site of the origin of the abnormal involuntary movements. Since neither operation nor ventriculography were carried out in those three cases, no further comment will be made, as it would not be of any value either for or against our hypothesis.

General Comment and Conclusions

We of course realize perfectly well that the cases presented here in some detail cannot serve as a foundation for truly binding conclusions, if for no other reason than because their number is too small. However, may they not serve as a pretext for further investigation? We hope that they may, since according to Jackson, "an hypothesis, otherwise a supposition, is not a conclusion but only the starting point for methodical observation and experiment, the endeavours being not only to prove it, but to disprove it".

We believe that diffuse damage to the brain, as commonly demonstrated by E.E.G. in patients suffering from the combination of the two syndromes under discussion, may result from injury, sustained at birth or later, infection, intoxication, or some other pathological factor. This diffuse damage, however, is not enough to provoke epilepsy. There always must be, and frequently we have been able to demonstrate its presence by modern means of investigation, somewhere in the brain a so-called epileptogenic focus. We knew its bio-electrical appearance, but to what kind of a lesion it actually corresponds, we do not know. It is true that Jasper in 1954 reminded us that for Jackson the basic physiological and chemical change underlying the initial discharge is probably the same in all cases, although the pathology may vary widely. Does this help us in the understanding of the nature of the harmful or epileptogenic focus?

We postulate, then, and after all our two cases seem to point to the reasonableness of such a supposition, that in cases with epileptic seizures and abnormal involuntary movements the first are caused by a separate pathogenic focus, localized in one or other region of the brain, while the abnormal involuntary movements are due to a diffuse involvement of the central nervous system (Chorobski, 1957 and 1961).

Here, we can but summarize our ideas very briefly. First, we draw your attention to the fact that intracranial tumours of any nature and location quite often provoke the appearance of "classical" syndromes, commonly attributable to involvement of the extrapyramidal system. This view is based on personal observation in 14 cases and on reports in the literature. Contrary to what is generally observed in cases of abnormal involuntary movements associated with birth injury, infection, or intoxication of the brain, the abnormal involuntary movements caused by brain tumours disappear after the removal of their cause, even though no paresis or paralysis of the extremities is produced. Further, the improvement of the motor activity, observed in the brain tumour cases, is often accompanied by a return of a more or less normal electrical activity of the brain. Such observations are of considerable interest.

In four of these 14 cases, the abnormal involuntary movements were concomitant with epileptic seizures. The most important point, however, is that after the tumour has been removed the epileptic seizures may either disappear simultaneously with the involuntary movements or they may not, thus supporting our assumption that the pathomechanism of these two pathological phenomena is not necessarily the same.

The cessation of the abnormal involuntary movements after the tumour has been removed, and even following simple incision of the dura, *i.e.*, a sudden change in the intracranial pressure, seems to confirm our idea of a functional rather than an anatomical cause of these movements. It is postulated, therefore, that the "derailment" of the innervation normally necessary for the maintenance of proper muscle tone and for the performance of a normal motor action, or of both, is brought about by stimuli coming from so-called reverberating chains of neurones. These stimuli interfere with the smooth cooperation of the pyramidal and extrapyramidal nervous systems, *i.e.*, with the *conditio sine qua non* of any normal motor activity. This interference takes place at the moment when the afferent nervous system is "busy" conducting the nervous impulses necessary for starting and controlling that activity.

We believe that this harmful action of chains of

neurons, located mainly within the plexiform layer of the cerebral cortex, or perhaps in the reticular formation of the brain-stem also, is brought about by their interfering with the nervous systems necessary for the performance of any motor action and may consist of an inopportune and/or inordinate emission of excitatory, and/or inhibitory stimuli which thus disorganize the proper maintenance of the muscle tone, and the performance of normal motor activity. These, as it were, extrasystemic stimuli may play upon some special nervous circuits, located in the midbrain, the malfunction of which results in, as some recent investigations tend to suggest, a Parkinsonian tremor. They may also act on the spinal gamma system which, of course, is responsible for muscle tone and is prerequisite for alpha system activity.

The cause which brings into play the reverberating neuronal chains, and produces the disturbance in the dynamics of the nervous system, may well be found in a case of brain tumour in the tumour's direct pressure upon the relevant nervous circuits or indirectly in the action of the tumour on them through the interference with the blood supply or oxygenation of the chains, intoxication of the brain by products of tumour metabolites. The same mechanism is probably at play in cases of abnormal involuntary movements of other aetiology.

And so, we come to the end of this communication which should be accepted as a kind of provocation to further study. We find some justification in suggesting this idea in view of Huxley's statement that the anticipation of Nature "by the invention of hypotheses even based on incomplete deductions . . . has proved itself to be a most efficient, indeed an indispensable instrument of scientific progress" (Science in the Reign of Queen Victoria, v.3).

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NARCOLEPSY IN IDENTICAL TWINS

BY

NORMAN W. IMLAH

From the Uffculme Clinic, Birmingham

Narcolepsy has been observed in chronic encephalitis, cerebral arteriosclerosis, brain tumour, and following trauma, but when these cases are excluded there remains a group without demonstrable brain pathology. The existence of this idiopathic group has been a controversial subject. Among the more impressive evidence is that suggesting a hereditary factor in idiopathic narcolepsy. To date this evidence has not contained an account of the condition in identical twins, and the existence of such a case is, therefore, reported.

The case came to our notice because one of a pair of twins was referred for psychiatric opinion.

The patient a man, aged 28, was admitted for full assessment and at the same time the twin brother was investigated. The monozygotic origin of the twins was shown by application of the similarity diagnosis (Stern, 1950). The following criteria of identicality were applied: (1) Striking similarity in general appearance, and (2) essential identity in (*a*) hair colour, (*b*) hair texture, (*c*) hair form, (*d*) eye colour, (*e*) skin colour, (*f*) amount and distribution of body hair, (*g*) features of nose, lips, chin, and ears, (*h*) type and proportions of hands and fingers, (*i*) height and weight.

In appearance both were 6 ft. in height, broadly built, black-haired, and sallow-complexioned. The hands and feet were large, and the jaws were overdeveloped giving a rather acromegaloid appearance to the face. The physical similarities were supported by repeated E.E.G. records which showed the basic similarities expected in identical twins.

Their father was interviewed for confirmation of family and early history. He was an ex-professional boxer, of good intelligence.

Case Reports

The family history of both parents was negative for narcolepsy, epilepsy, and mental defect; the twins were their sole offspring. The birth and development of the twins was normal. As children they had measles, whooping cough, and chickenpox without complications, and revealed nothing untoward until the appearance of symptoms of narcolepsy.

The Patient.—W. first experienced symptoms at the age of 13. These began with a tendency to fall asleep at school, particularly when he sat near radiators or in a stuffy classroom. He found increasing difficulty in getting up in the morning, and after arousal remained in a dazed state for some time so that he was invariably late for school. At 14 he became an apprentice toolmaker and was in frequent difficulty, sleeping so long some days that he missed work altogether. At the same age he took up amateur boxing, but despite good natural ability he became exhausted after one round and thereafter could do little more than defend himself. He found training excessively fatiguing and at the age of 19 he had to give up boxing. (Levin, 1959, described the case of a boxer being unable to continue boxing on account of narcolepsy, and suggested that cataplexy occurs in the wake of an undisguised or symbolic aggressive impulse.)

At 18, because his work record was so poor, he left toolmaking and joined the Army. During two years in the Army symptoms increased, but the nature of the condition remained unrecognized. He was frequently in trouble for falling asleep during Army duties. Before entering the Army he had frequently experienced "*cataplexie du reveil*", but now cataplectic attacks during the day became an additional feature. These attacks were of the spontaneous variety and he does not recall that they were provoked by emotion. They took the form of momentary feelings of weakness with inability to speak or move. Attacks of this type occurred frequently during Army service, but since he left the Army have gradually lessened in frequency and had not occurred recently.

After two years he was given a normal discharge and attempted a return to toolmaking, but again failed to adapt himself. From then onwards his work record was dismal, and he attempted a wide range of jobs, including those of production engineering, car assembly, coal heaving, builder's labourer, painter, scrap merchant, and door-to-door canvasser. Some jobs he gave up because he felt bored or exhausted; in others he fell asleep at the job and was sacked. A number of employers mistook his illness for epilepsy and he was dismissed.

Only at the age of 23 was his illness diagnosed by a neurologist, and he was treated with amphetamine. This caused a lessening in the number of attacks but no improvement in work record.

He married at 25 and when seen had a 7-month-old son. His marriage was happy apart from the anxiety created through his failure to keep in employment, and

his wife's worry over his frequent nightmares from which he would awaken, screaming and shouting. On admission he was on 50 mg. dextro-amphetamine daily, but despite this was having daily attacks of narcolepsy, and nightmares every night.

There were no abnormal findings on physical and routine blood examinations, and skull radiographs were entirely negative.

Under observation as an in-patient he did not reveal overt neurotic traits, and psychiatric investigations showed no definite neurotic symptoms.

Twin Brother.—J. developed symptoms at 13, a few months later than his brother. He, too, experienced difficulty in morning waking and a tendency to fall asleep in a stuffy classroom. He left school at 14, and with his brother began work as an apprentice toolmaker. Although he had difficulty in getting to work in time, his symptoms were never as severe as those of his brother, and he was able to adapt better to working conditions. His record as an apprentice, although not perfect, was acceptable to his employers.

Like his brother he began amateur boxing, but gave up after 15 months on the pretext of a nose injury. He did not, however, suffer from the same fatigueability in the ring, but was more than ordinarily exhausted by training.

At 20 he joined the Army, and for two years of military service symptoms were much worse. He was often in trouble for falling asleep in the classroom, and his only attacks of cataplexy occurred in this period. One night, sleeping in a makeshift bed, he remembers vividly waking three times during the night, on each occasion terrified, but quite unable to shout or move. He had another attack of cataplexy while on guard duty. On this occasion he suddenly felt weak, unable to move or speak, and he thinks this lasted several seconds. He does not recall that this attack was precipitated by any emotion, and the attack appears to have been spontaneous.

On leaving the Army he returned to toolmaking with his former employer and since then has been symptom-free, excepting for frequent vivid nightmares. He has never received treatment for his narcolepsy. He is happily married, and now considers himself a normal, average person.

Psychological Comparisons

On the Bellevue oral scale, W., the patient, had a somewhat higher I.Q. than his brother (117 as against 111). This was accounted for by higher scores on digit span and on similarities.

On the Rorschach test, W. was more productive with 36 responses as against 28. Only two responses coincided. J. showed some stereotypy and a rather narrower range of ideas with very little interest in colour. W. brought colour more into his responses and had nearly three times as many responses to the last three (coloured) cards. Of the two Rorschach protocols, W's showed rather less pathology.

Electroencephalographic Comparisons

Recordings were made and repeated on both patients. The records showed the basic similarity expected in identical twins. Episodic theta activity was seen in both records, slightly increased after overbreathing, and more marked in W. The records were extremely alike except that W. had more slow activity and slightly slower slow.

The theta was typical of the changes found in drowsiness, or drifting. Daly and Yoss (1957) have given a very clear account of such changes. They consider that the E.E.G. is within normal limits in narcolepsy, but shows repeated changes due to drowsiness. The records of the twins were in accordance with this view.

Discussion

The existence of a possible hereditary factor in idiopathic narcolepsy gained prominence when Krabbe and Magnussen (1942) reviewed all the cases in the literature and found that 54 of the cases belonged to 19 families, with from two to eight narcoleptics in each family. They postulated that inheritance is linked to a single dominant gene with relatively slight penetrative power.

This theory has been supported by a more recent report by Daly and Yoss (1959) on a family with narcolepsy. Investigations of this family disclosed a total of 12 instances of narcolepsy in three generations. The third generation contained one set of monozygotic twins, neither of whom were, however, afflicted with narcolepsy. Daly and Yoss suggest that the disorder in this family was transmitted by a single dominant factor with a high degree of penetrance. Daly (personal communication) has seen several instances of dizygotic twins in which only one was afflicted by narcolepsy, but has not observed narcolepsy in any monozygotic twins.

The case described here appears to be the first recorded one of its kind, and lends support to the idea of a genetic transmission of idiopathic narcolepsy. The basic difference that existed, in severity of affliction, between the twins did not seem sufficient to explain the whole difference in outcome. Psychological factors appear to have had a modifying effect on the course. Two factors may have been of importance. W. appeared to be more adventurous, more extrovert, with more drive, and with a wider range of interests. He was thus more easily bored by routine and unimaginative work. In addition, it was shown at occupational therapy, and confirmed at an industrial rehabilitation unit, that he had poor manual dexterity to such a degree that work with his hands must have given very little satisfaction; this may have contributed to his earlier failure to become a toolmaker like his brother.

It is satisfactory to conclude by recording that W. is now employed as a milk roundsman, and, despite reduction of dextro-amphetamine to 25 mg. daily, he seldom falls asleep during the day, and has very few nightmares.

Summary

Case reports are presented on a set of identical twin brothers with idiopathic narcolepsy.

Psychological and electroencephalographic comparisons are shown.

Genetic implications and psychological differences are discussed.

I wish to acknowledge the cooperation of Dr. H. Halstead, senior clinical psychologist at Uffculme Clinic, who carried out the psychological tests, interpreted the results, and acted as vocational adviser; also the co-operation of Dr. P. M. Jeavons, consultant psychiatrist at All Saints Hospital, Birmingham, who arranged the E.E.G. recordings, interpreted the records, and provided the opinion expressed on these records.

I would also like to thank Dr. J. J. O'Reilly, Medical Director of Uffculme Clinic, for permission to publish this case.

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OBSERVATIONS ON THE CAROTID BRUIT

BY

W. B. MATTHEWS

From the Derbyshire Royal Infirmary

The reported results of surgical treatment of carotid atheroma indicate that disobliteration of an occluded vessel is relatively safe but unlikely to produce much benefit, whereas operating on a stenosed artery is more hazardous but also more rewarding. This naturally throws great emphasis on the diagnosis of carotid stenosis as opposed to occlusion, a difficult clinical exercise. Patients with slight symptoms, those most likely to benefit, often resist the suggestion that they enter hospital for unpleasant investigations and the physician may well have qualms in recommending that they do so. The natural history of untreated carotid stenosis is unknown and angiography is not without risk. However, there is one physical sign which has been claimed to be of value in distinguishing between stenosis and occlusion, the presence of an arterial bruit. Edwards, Gordon, and Rob (1960) stated that "In the absence of a conducted murmur from the heart, a systolic bruit heard over the artery is reliable evidence of a partial stenosis'. Peart and Rob (1960) further state that this bruit was present in 59 of 103 cases with proved stenosis and that "In no case of complete internal carotid occlusion was this murmur heard". In my own much smaller experience the relation between the bruit and the arterial disease has been more complex.

This paper is not a statistical study but a description of illustrative cases. No example of internal carotid stenosis producing a bruit will be described as this undeniably occurs and requires no further demonstration. In none of the patients described was there a cardiac murmur, anaemia, or subclavian bruit, all possible causes of confusion. The bruits observed were loud harsh noises not obviously affected by posture of the head or pressure of the stethoscope.

Case Reports

Case 1 (DRI 28619).—A man of 52 was admitted to hospital in November, 1955, with a two weeks' history of progressive left hemiplegia. His condition deteriorated over the next 10 days and he became mentally confused, had a severe hemiplegia, hemianopia, and marked sensory loss. The progressive course suggested a cerebral tumour but a ventriculogram (Mr. G. Clark-Maxwell) was normal. He gradually improved but was left with a residual hemiparesis. In 1957 he developed focal fits in the left upper limb. A bruit was heard over the right carotid. Fig. 1 shows that this was loudest high in the neck, and Fig. 2 that it was entirely systolic, the second heart sound being visible in the tracing at the end of the bruit. Carotid angiography (Fig. 3) showed occlusion of the right internal carotid. The external carotid, although not tightly stenosed, is obviously narrowed at its origin. The bruit persists although it has become softer. The left carotid was not investigated.

Case 2 (DRI 217368).—In January, 1960, this man of 51 sustained a left hemiplegia from which he recovered in the course of a month. In May, 1960, the right upper limb became weak and he was admitted to hospital. He was dysarthric, slightly demented, and the right upper limb was weak. A bruit was heard over both carotids and that on the right is illustrated in Figs. 4 and 5. It was maximal high in the neck and was entirely systolic. Angiography showed stenosis of the left common, and of the internal and external carotid arteries. On the right (Fig. 6) the internal carotid was occluded with stenosis of the external.

Case 3 (DRI 74885).—This man of 54 was first seen in September, 1959, after an episode of slight dysgraphia from which he had recovered. He had slight weakness of the right side of the face and a loud bruit over the left carotid. He refused admission to hospital. In March, 1960, he sustained a left hemiplegia but recovered rapidly and soon afterwards was admitted. The bruit on the left was still present and showed the same characteristics as in the other two patients (Figs. 7 and 8). Angiography showed occlusion of the left internal carotid and probably some narrowing of the external (Fig. 9). On the right good filling of the common and external carotids was obtained but no dye entered the internal carotid. Some dye entered the carotid sheath and as this sometimes produces artefacts it could not be concluded with certainty that the internal carotid was occluded on this side also. Following angiography the patient again developed a left hemiparesis but has now recovered and is at work.

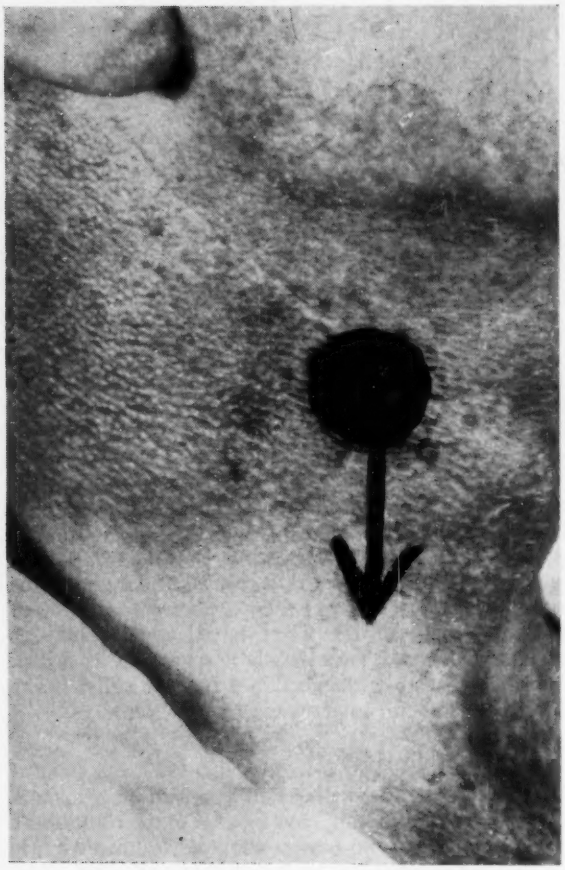

FIG. 1.—Site of bruit in Case 1. In this and subsequent figures the circle marks the point at which the bruit was loudest and from which it was recorded. The arrow marks the approximate area in which it was clearly audible.

FIG. 3.—Right carotid angiogram in Case 1 showing occlusion of the internal carotid and narrowing of the external carotid.

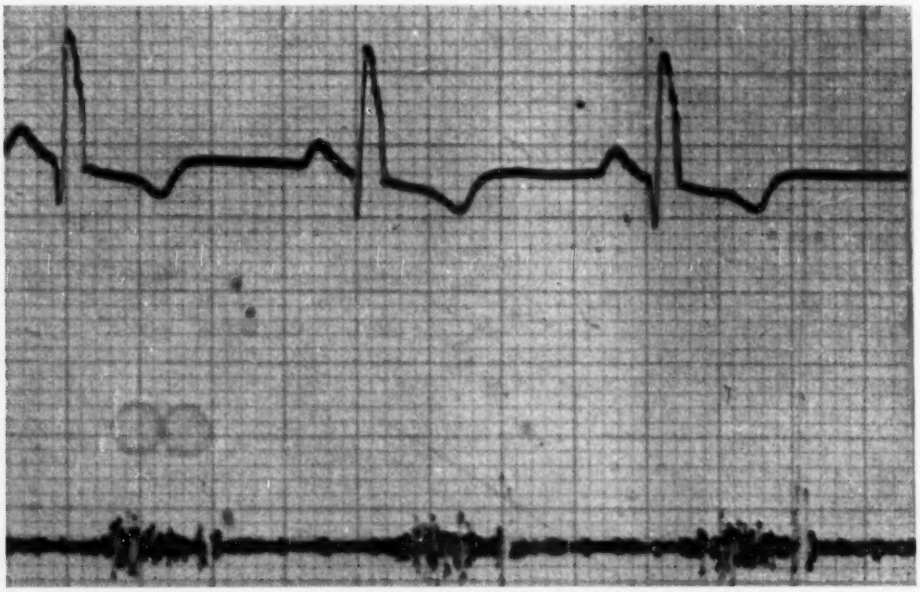

FIG. 2.—Phonocardiogram of the bruit in Case 1. The E.C.G. and carotid bruit are recorded simultaneously. The second heart sound is visible at the end of the bruit.

FIG. 4

FIG. 4.—Site of the bruit in Case 2.

FIG. 5.—Recording of bruit in Case 2. The second heart sound is again visible.

FIG. 6.—Right carotid angiogram in Case 2 showing occlusion of the internal carotid near its origin and localized stenosis of the external carotid.

FIG. 6

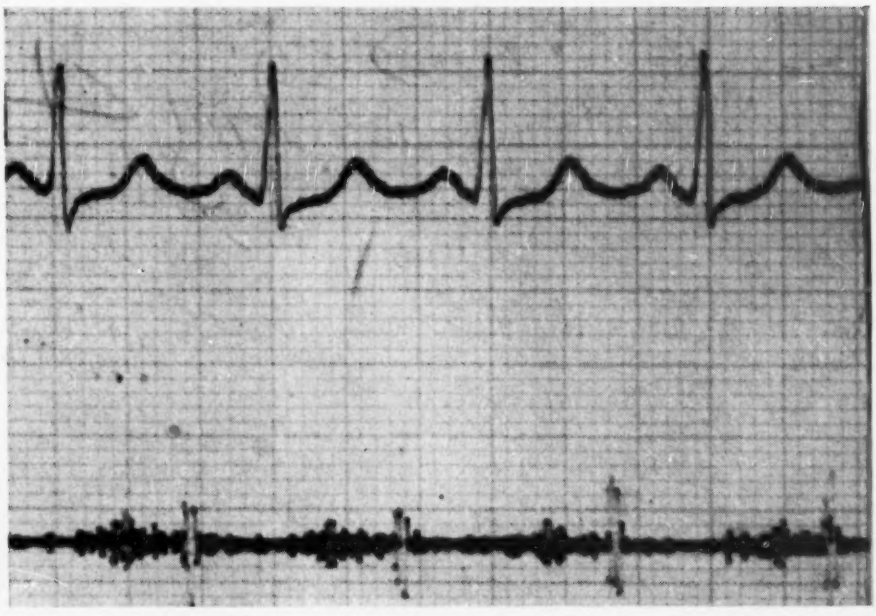

FIG. 5

FIG. 7.—Site of bruit in Case 3.

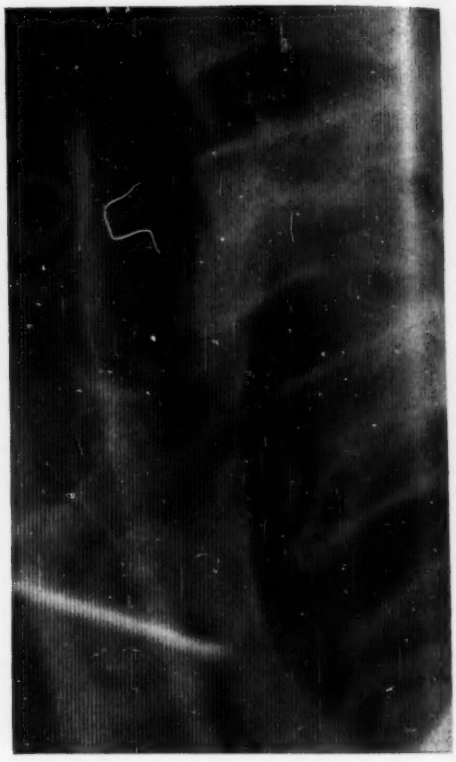

FIG. 9.—Left carotid angiogram in Case 3 showing occlusion of the internal carotid and apparent relative narrowing of the first centimetre of the external carotid.

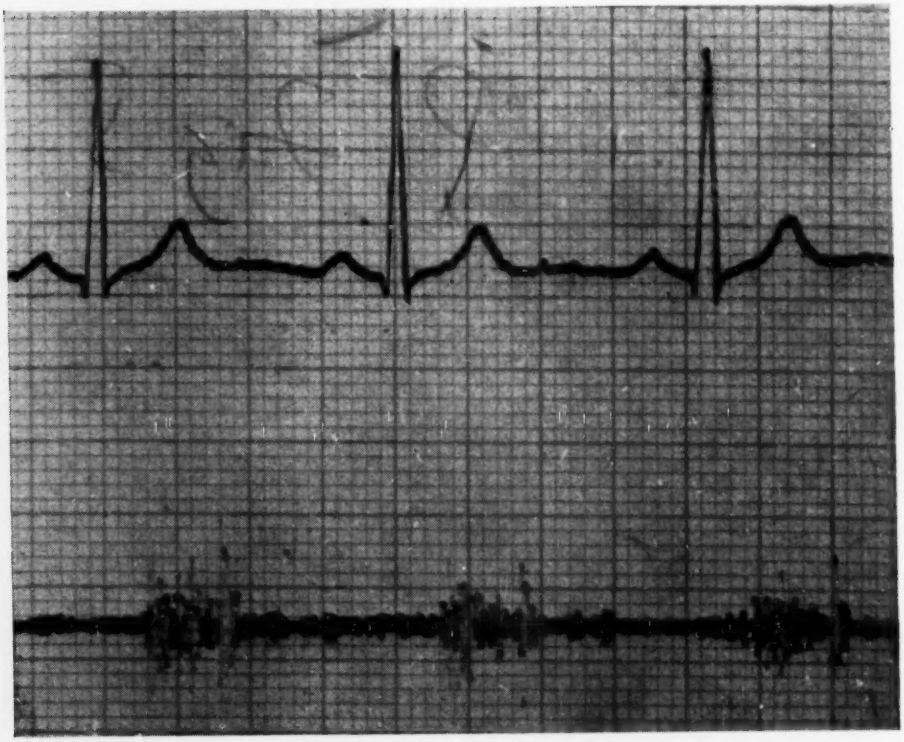

FIG. 8.—Recording of bruit in Case 3.

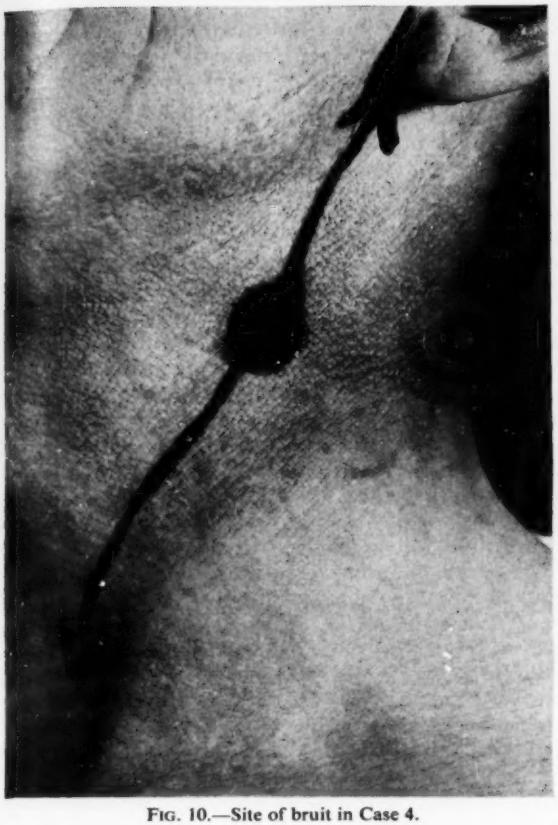

FIG. 10.—Site of bruit in Case 4.

FIG. 12.—Left carotid angiogram in Case 4 showing gross stenosis of the external carotid and a normal internal carotid.

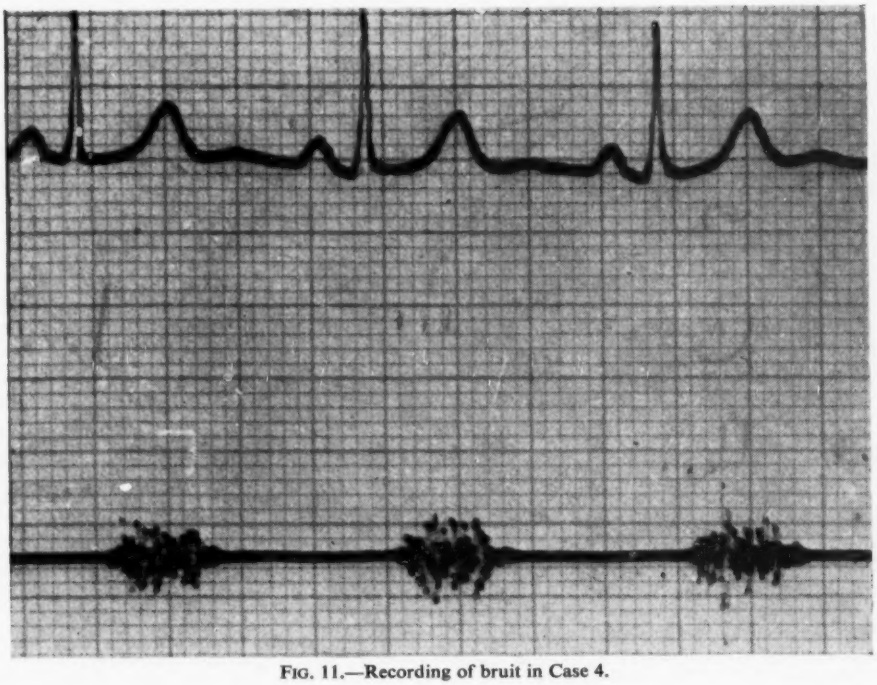

FIG. 11.—Recording of bruit in Case 4.

Case 4 (DRI 212716).—A man of 51, admitted to hospital in November, 1959, gave a complicated history in which he described two distinct types of transitory attack. In one type he would develop weakness of the right lower limb, and in the other, loss of the lower half of the visual field in the right eye. On one occasion he had lapsed into unconsciousness. In quiet surroundings he was aware of a pulsating, roaring noise in his left ear. A loud bruit was audible over the left carotid (Figs. 10 and 11). The patient asked if he might listen to this through a stethoscope and then stated that this was the noise he could hear himself without artificial aids. He was transferred to the care of Dr. Ian Mackenzie at Guy's Hospital, London, where angiography was carried out. This showed stenosis of the right internal carotid and of the external carotid on the left, the side of the bruit (Fig. 12). After an operation for disobliteration of the right internal carotid artery the patient became free from symptoms, but there is now a bruit on the right.

Discussion

The first three patients demonstrate that a bruit may be present over a completely occluded internal carotid artery, the external carotid being narrowed to varying degrees. These murmurs completely fulfilled the criteria laid down by Peart and Rob (1960) as being characteristic of internal carotid stenosis, loudest in the region of the bifurcation of the artery and confined to systole. These authors mention one patient with a similar bruit associated with stenosis of the external carotid alone, and this is illustrated by my fourth patient in whom the bruit was on the side of the external stenosis, the stenosis of the internal carotid on the other side being silent.

I am, however, doubtful whether arterial stenosis is the sole cause of bruits in arterial disease. The possible role of increased blood flow through collateral vessels is illustrated by the following case.

Case 5 (DRI 218609).—A woman of 36 was admitted with a subarachnoid haemorrhage. No bruit was audible over the skull or carotids. Bilateral carotid angiography showed a small carotid aneurysm on the right. The common carotid on that side was ligated (Mr. R. H. Shephard) but doubts were cast on the full efficacy of this by the immediate appearance of a bruit over the ligature. At a second operation to ligate the internal carotid it was found that the original ligature had permitted some blood flow although the temporal pulse had been absent. After the second operation no bruit was audible over either carotid. Seven days later, however, a bruit became audible over the left carotid (Fig. 13) and has persisted for six months.

This bruit was not distinguishable in any way from those observed in the patients with arterial disease in the neck. Atheroma cannot, of course, be entirely excluded as a cause in this patient but must be regarded as extremely unlikely and I suggest that increased blood flow in the normal vessel is a more probable cause. Further observations on patients with carotid ligations are in progress.

From these examples it must be concluded that there is no simple relationship between stenosis of the internal carotid artery and a systolic arterial bruit. I believe that such a bruit may be important evidence of atheroma of the vessels in the neck but that angiography is regrettably necessary for the accurate diagnosis of occlusive carotid artery disease.

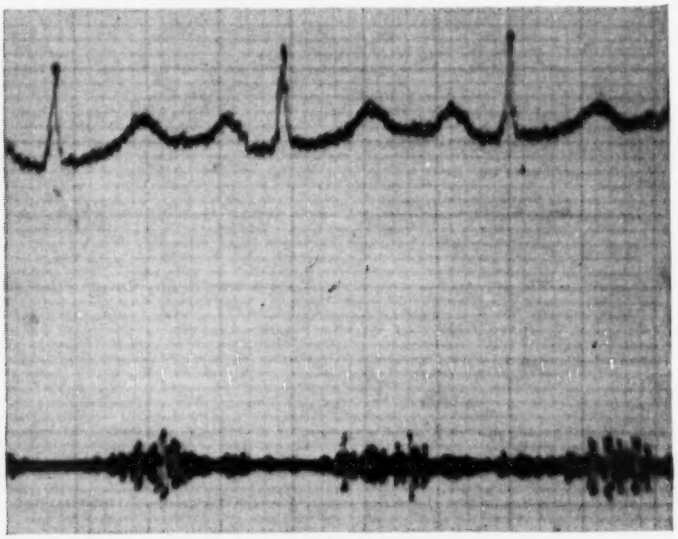

FIG. 13.—Recording of bruit in Case 5. Some respiratory noise is also recorded and the second heart sound is not visible but the timing of the bruit does not appear to differ from that in the preceding cases.

Summary

Three patients are described with a carotid bruit on the same side as a completely occluded internal carotid artery and one patient with a bruit over a stenosed external carotid and an apparently normal internal carotid. The possible roles of external carotid stenosis and of increased blood flow in collateral vessels are discussed.

I wish to acknowledge with thanks Dr. R. D. Hoare's permission to reproduce the angiogram in Case 4 and Mr. R. H. Shephard's permission to describe Case 5.

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HERPES ZOSTER AND THE LANDRY-GUILLAIN-BARRE SYNDROME

BY

J. D. E. KNOX, R. LEVY, and J. A. SIMPSON

From the Neurological Unit of the Department of Medicine, University of Edinburgh, the Northern General Hospital, and the Royal Infirmary, Edinburgh

In 1900 Head and Campbell described the pathological features in 20 cases of herpes zoster. They showed that the main sites affected in this disease are the posterior root ganglia and the ganglia of certain cranial nerves. Associated paresis was originally described by Broadbent (1866) and Waller (1885) and Lhermitte emphasized that the nervous system may become more extensively involved (Lhermitte and Nicolas, 1924; Faure-Bealieu and Lhermitte, 1929; Lhermitte and Vermès, 1930). Cases associated with limb weakness may be broadly classified into four main groups: (1) Those in which there is flaccid paresis localized to the region affected by the rash, and attributed to involvement of the anterior root in its course past the necrotic posterior root ganglion (Denny-Brown, Adams, and Fitzgerald, 1944). They are well recognized and have recently been reviewed by Kendall (1957). (2) Those in which there is spastic weakness and sensory impairment with a definite upper level. These are due to involvement of the spinal tracts and may be related to the demyelinating diseases (Alajouanine and Bernard-Griffith, 1931; Gordon and Tucker, 1945; Kendall, 1957; McAlpine, Kuroiwa, Toyokura, and Araki, 1959). (3) Those in which there is spastic weakness of one or more limbs, occasionally with sensory disturbance and associated with disorders of consciousness and other signs pointing to involvement of the brain substance (Thalhimer, 1924; Gundersen, 1925; Faure-Beaulieu and Lhermitte, 1929; Lhermitte and Vermès, 1930; Schiff and Brain, 1930; Biggart and Fisher, 1938; and Gordon and Tucker, 1945). (4) Those with widespread flaccid paresis and varying degrees of sensory disturbance developing a short time after the rash and showing the features of peripheral neuritis or polyradiculitis.

Since only a few cases belonging to this last group have been described, we think it worth while reporting three which we have recently encountered in Edinburgh.

Case Reports

Case 1.—In June, 1959, J.N. a 69-year-old engineer-mechanic developed a crop of blisters over the medial aspects of the left forearm. He complained of constant gnawing pains in the affected region and, although the blisters crusted and disappeared over two weeks, this pain persisted. A month later, his left hand became numb, and he began to have difficulty in gripping, which progressed until he had to give up work one week later. In August he had a sudden attack of deafness in the right ear associated with tinnitus and vertigo. The whole episode lasted only about an hour. He was admitted for investigation on August 20, 1959.

On examination, the cranial nerves were intact and the fundi were normal. He had slight bilateral middle ear deafness, more marked on the right side. There was scarring in the distribution of the left first thoracic nerve. The skin of both hands was thick, shiny, and atrophic. There was wasting and fasciculation of the triceps and of the first dorsal interosseous muscles on both sides. On the left, the shoulder girdle muscles, the deltoid, and the long extensors of the wrist and of the fingers all showed wasting. The tendons of the long extensors of the fingers of the right hand were shortened to such an extent that passive closure of the fist was impossible.

Widespread weakness was noted in the upper limbs and although there was no wasting in the legs, both tibialis anterior muscles were weak. All tendon reflexes were greatly diminished; abdominal reflexes were present and the plantar responses were flexor. There was an area of diminution of sensation to pin prick and light touch over the scarred area and along the medial border of the foot. Proprioception was intact. The muscles were not unduly tender.

Investigations.—The blood contained 14.0 g. haemoglobin per 100 ml. (Sahli), 6,800 leucocytes per c.mm. and had a sedimentation rate of 5 mm. in the first hour (Westergren). The urine contained no protein or sugar. A chest radiograph was normal and the cervical spine radiograph showed minor degenerative changes. On August 21 the cerebrospinal fluid (C.S.F.) pressure was 150 mm. of water with free rise and fall on jugular compression with the neck in extension or flexion. The fluid was clear and colourless. It contained 45 mg.

TABLE I

ELECTROMYOGRAPHIC FINDINGS IN CASES 1, 2, AND 3

Case	Date	Muscle	Fasciculation	Fibrillation	Polyphasic Units	Maximum Voluntary Activity*
1	26.8.59	L. first dorsal interosseous	—	+	—	+
		R. tibialis anterior	—	+	—	++
	14.10.59	R. first dorsal interosseous	—	+	—	+
		R. tibialis anterior	—	+	—	+
2	13.11.59	L. first dorsal interosseous	++	++	+	++
		L. tibialis anterior	+	—	+	++
	19.1.60	L. first dorsal interosseous	+	—	+	+++
		L. tibialis anterior	+	—	+	+++
3	27.1.60	R. triceps	—	—	—	++

* +++ Normal interference pattern ++ Reduced interference pattern + Discrete units only — No voluntary activity

protein per 100 ml., 3 cells per c.mm., and gave a negative Lange curve.

Electromyography on August 26 showed changes suggestive of neuropathy (Table I).

Progress.—A week later, the weakness in the anterior tibial muscles on both sides had increased considerably and the left hamstrings were now affected. The weakness of the upper limbs was unchanged. The tendon reflexes were now absent. During the following week his condition remained static and he was discharged home at the end of August.

He was admitted for further assessment on October 6. Two weeks previously he had had another brief attack of vertigo and tinnitus, severe enough to force him to bed for the day. In addition, he complained of difficulty in walking and said that his feet 'came down with a bang'.

Examination revealed that weakness of all limbs had become slightly more marked. There was now wasting and fasciculation in the left tibialis anterior, and he had developed a 'high-stepping' gait. The tendon reflexes were still absent and the plantar responses were flexor.

Lumbar puncture was repeated on October 12. The cerebrospinal fluid contained no cells and 50 mg. protein per 100 ml. Lange and Wassermann reactions were negative. Electromyography on October 14 showed little change (Table I) and nerve conduction studies, using the method of Simpson (1956, 1958), confirmed the diagnosis of peripheral neuritis (Table II).

On October 16, Prednisolone was started. The initial dose of 60 mg. daily was reduced to 40 mg. daily on the 19th, and the patient was discharged to a convalescent home on October 22 on this maintenance dose. On November 1, the dose of steroid was further reduced to 30 mg. daily. Although he felt better, there was no objective change. He died suddenly while running for a bus on November 21, and no necropsy was performed.

Case 2.—A.B., aged 54, developed severe right-sided herpes zoster ophthalmicus about May 24, 1959. Because of corneal ulceration, he was admitted to the Ophthalmic Department, but was discharged after six days when his condition appeared to be settling. About six weeks later he developed gradual loss of power in both legs, and tingling in both feet. Within a few days the tingling spread to both hands which also became weak. His condition slowly deteriorated, so that by the time of admission on July 30 he was unable to sit up unaided.

On admission he was apyrexial. There was scarring and residual crusting of the skin over the distribution of the ophthalmic division of the fifth nerve and a small corneal opacity on the right side. Coarse, unsustained nystagmus was present when he looked to the left. There was marked generalized weakness of the limbs and trunk other than the muscles of respiration. The tendon and abdominal reflexes were absent. The plantar responses were flexor. Vibration sense was absent distal to the knees and elbows, but all other modalities of sensation

TABLE II

NERVE CONDUCTION STUDIES

Case	Date	Nerve	Stimulation at	Muscle*	Length of Nerve (cm.)	Latency of Response (in msec.)†
1	17.10.59	R. ulnar	Elbow	Abd. dig. min.	32	21
		R. ulnar	Wrist	Abd. dig. min.	8	10·5
2	13.11.59	L. ulnar	Elbow	First dors. interos.	35	14
		L. ulnar	Wrist	First dors. interos.	8	8·5
	19.1.60	L. ulnar	Elbow	First dors. interos.	37	15
		L. ulnar	Wrist	First dors. interos.	10	6·5
		R. ulnar	Elbow	First dors. interos.	35	15
		R. ulnar	Wrist	First dors. interos.	9	7·5
		L. median	Elbow	Abd. poll. brev.	30	12
		L. median	Wrist	Abd. poll. brev.	6	8·5
3	25.1.60	R. ulnar	Elbow	First dors. interos.	33	9·5
		R. ulnar	Wrist	First dors. interos.	8	5

*Belly-tendon surface electrodes.

†Normal latency for each nerve and muscle tabulated does not exceed 5·0 msec. and 12 msec., stimulating at wrist and elbow respectively.

were normal. The muscles were not unduly tender. Both hands and feet perspired profusely.

Investigations.—On July 31 the blood contained 13.3 g. haemoglobin per 100 ml. (oxyhaemoglobin method), 8,200 leucocytes per c.mm., and had a sedimentation rate of 10 mm. in the first hour (Westergren). There was no protein or sugar in the urine. Radiographs of the skull and chest were normal. Lumbar puncture showed that there was no block to C.S.F. flow with the neck flexed or extended. The C.S.F. was clear and colourless, and was sterile on culture. It contained 3 lymphocytes per c.mm., 97 mg. protein, and 67 mg. sugar per 100 ml. The Wassermann reaction was negative and the Lange curve was 122220000 in the cerebrospinal fluid. Serial changes in C.S.F. constitution are plotted in Fig. 1. The fluid

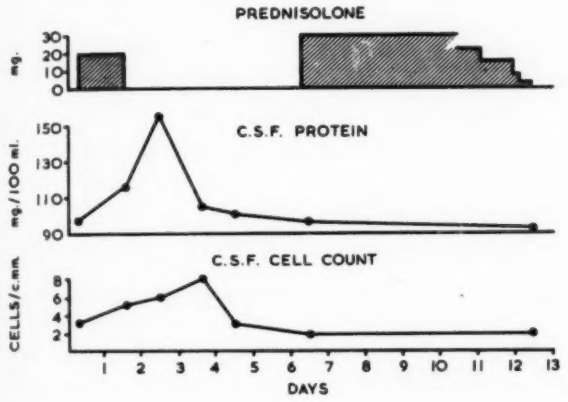

FIG. 1.—Cerebrospinal fluid protein and cell count and associated steroid dosage in Case 2.

was cultured on monkey kidney tissue. A virus was grown which was finally identified as being of the ECHO group, type 9. No virus was isolated from his stools.

Electromyography and nerve conduction studies on November 13 showed changes which were compatible with a diagnosis of polyneuritis (Tables I and II).

Treatment and Progress.—Despite Prednisolone (20 mg. daily starting on July 3), his condition continued to deteriorate slowly and muscular weakness increased. The steriod was, therefore, stopped after five days and high potency Parentrovite was given intramuscularly, but this also had no appreciable effect. He then developed a right pulmonary embolus from phlebothrombosis of leg veins and this was treated with anticoagulants and penicillin. On September 19 his neurological condition was unchanged. There was generalized wasting of muscles and fasciculation in the forearms, the hands, and the calves. A second course of Prednisolone (30 mg. daily) was started. Thereafter his condition improved, so that within four weeks he was able to walk unaided. He was finally discharged home at the end of October. When he was seen again on January 19, 1960, there was only slight residual weakness in the extensors of the wrists on both sides. The ankle jerks were absent and the other tendon reflexes were elicited with difficulty.

Electromyography and nerve conduction studies were repeated. These showed considerable improvement (Tables I and II).

Case 3.—Mrs. E. McC., a widow aged 65, had rheumatic mitral incompetence with associated atrial fibrillation. On January 27, 1958, she developed herpes zoster affecting the eleventh and twelfth thoracic segments on the left. This condition settled gradually, but on March 12 she noticed constant pain in the region of the left hip. The pain persisted, being worse at night, and a week later she suddenly developed weakness in the left leg. Next day she felt pins and needles in both hands, and the following day in both feet. By this time she was unable to walk because of weakness in both legs. A few days later she became incontinent of urine.

On examination on March 25 she was apyrexial. The cranial nerves were intact. There was widespread muscular weakness involving all limbs with pain on movement. The trunk and respiratory muscles were not affected. The tendon and abdominal reflexes were absent. The right plantar response was extensor. Exteroceptive sensation was impaired over the dorsum of the left foot and the finger tips of both hands. Vibration sense was absent in both legs. The muscles were not unduly tender.

Investigations.—The blood contained 13.7 g. haemoglobin per 100 ml., 7,600 leucocytes per c.mm., and had a sedimentation rate of 9 mm. in the first hour (Westergren). The urine contained a few pus cells and a trace of protein but no sugar. Radiography showed slight cardiac enlargement. Cerebrospinal fluid obtained by lumbar puncture (with normal manometric response) was sterile on culture. It contained 4 lymphocytes per c.mm., 162 mg. protein, and 69 mg. sugar per 100 ml. The Wassermann reaction was negative.

Treatment and Progress.—Prednisolone was given in a dose of 30 mg. daily starting on March 27, but the condition progressed and two days after the drug was started, she developed a partial paralysis of the right third cranial nerve with ptosis and slight diplopia. Thereafter she made a slow but almost complete recovery, and was discharged home on June 5.

A repeat lumbar puncture on October 21 gave normal C.S.F. containing 47 mg. protein per 100 ml.

Seventeen months later she was re-admitted with left hemiplegia, which was attributed to cerebral embolism. Neurological examination at this time revealed no sign of her previous illness apart from residual weakness of the right triceps.

She came to our notice at this time and electromyography and nerve conduction studies were carried out on January 25, 1960. The findings were considered to be within normal limits, but compatible with recent polyneuritis (Tables I and II).

Review of Cases Reported

Polyradiculopathy following herpes zoster was first described by Wohlwill (1924). This case, however, was by no means clear-cut as the patient had a positive Wassermann reaction and post-mortem

TABLE III

CLINICAL FEATURES AND CEREBROSPINAL FLUID FINDINGS IN THE CASES COLLECTED FROM THE LITERATURE TOGETHER THOSE IN OUR OWN CASES

Author	Sex	Age	Site of Eruption	Latent Period	Site of Paresis	Sensory* Disturbance	Cranial Nerve Involvement	Other Features	C.S.F.		Onset	Course Outc
									Cells (per c.mm.)	Protein (mg./100 ml.)		
Wohlwill (1924)	F	44	R. Th.5	Two weeks	Four limbs	Yes	No	Wassermann reaction +ve	'Normal'†	'Raised'†	Acute	Death in
Schuback (1930)	F	62	R. Th.3	Seven days	Four limbs	?	No	—	?†	?†	Acute	Death in
Riser and Sol (1933)	M	30	L. Th.3-5	Two months	Four limbs	Yes	No	Swelling and redness of fingers, urinary symptoms	'Normal'†	1,750	Insidious	Recovery areflexia
Gilpin *et al.* (1936)	M	52	R. Trig. (first d.)	'Few days'	Bilaterally face and four limbs	Yes	Bilaterally seventh	Dysarthria	'Normal'†	'Raised'†	Subacute	Death in months
Maggi *et al.* (1956)	M	68	L. Th.4	One month	Four limbs	Yes	R. eighth	—	'Normal'†	'Normal'†	Insidious	Partial re four mo
Friart and Jeanty (1956)	F	72	L. L.5	?	Both legs	Yes	No	Incoordination and stupor, bowel and bladder symptoms, postural hypotension	25 max.	3,300 max.	Subacute	Recovery months
Stammler and Struck (1958)	F	66	L.3	Three days	Four limbs	Yes	Bulbar	—	430	5,000	Acute	Death in tive heart
Pálffy and Balázs (1958)	F	63	R. Th.6-7	Two months	Four limbs	Yes	No	Unsteady legs	9	146	Insidious	Recovery months
Pálffy and Balázs (1958)	F	53	L. Th.11-12	Seven days	Four limbs	Yes	Bulbar	—	14	24	Acute	Death in
Duperrat and Pringuet (1958)	M	53	R. Th.2-3	Two days	Four limbs	Normal	R. seventh	—	3·8	480	Acute	Death in
Present Series												
J.N.	M	69	L. Th.1	Two weeks	Four limbs	Yes	No	Atrophic skin and contractures	3	50	Insidious	Death, pu unrelated months
A.B.	M	54	R. V. first div.	Seven weeks	Four limbs	Yes	No	Profuse sweating of feet, ECHO 9 virus in C.S.F.	8	89-150	Subacute	Recovery months
E.McC.	F	65	L. Th.11-12	Seven weeks	Four limbs	Yes	R. Third	Urinary incontinence, extensor L. plantar response	4	162	Acute	Partial re in three

*Other than those localized to site of eruption. †No values published.

evidence of syphilitic cardiovascular disease. Since that time nine further cases have been reported. The main features of these and of our own are shown in Table III. It will be noted that most cases occurred after the age of 50 years. This is probably merely an expression of the higher incidence of herpes zoster in the middle-aged and elderly. Both sexes were equally affected.

After the appearance of the eruption, there was a latent period varying from a few days to two months. This was followed by the neurological complications which progressed over a matter of hours (Wohlwill, 1924; Schuback, 1930), or, more gradually over a few days. The length of the latent period appears to be a good index of the severity of the disease: a short latent period (up to two weeks) was followed by a severe and fatal illness, while a long latent period (two weeks to two months) was followed by a mild illness. With one exception (Friart and Jeanty, 1956), all patients had paresis of the four limbs. Taterka and O'Sullivan (1943) and Halpern and Covner (1949) have drawn attention to a similar latent period for paralysis in the more common type where this is of limited distribution and usually anatomically related to the sensory disturbance.

For many of the cases, the nature and extent of the sensory involvement have not been recorded in detail so that it is impossible to give a comprehensive analysis. However, it would appear that they were very variable. In some cases they were purely subjective, consisting of paraesthesiae in the affected area; in others, objective disturbances were demonstrated ranging from mild hypoaesthesia to severe anaesthesia.

Cranial nerve involvement was seen in five cases. Gilpin, Moersch, and Kernohan (1936) and Duperrat and Pringuet (1958) reported bilateral facial palsy, Maggi, Meeroff, Cosen, and Hirschman (1956) unilateral nerve deafness, and Pálffy and Balázs (1958) severe bulbar symptoms. Our own Case 3 had a partial right third nerve palsy. In some instances there were changes suggestive of autonomic involvement. Thus, swelling and redness of the fingers was observed by Riser and Sol (1933), Friart and Jeanty (1956) recorded severe postural hypotension, and profuse sweating of the hands

and feet was noted in our second case. Case 1 developed atrophic skin changes and shortening of the extensor tendons of the fingers, an appearance rather similar to that seen in scleroderma.

The C.S.F. changes were variable. Usually, but not invariably, the protein was raised with a normal or slightly elevated cell count. The fluctuation in the C.S.F. protein in our second case is shown in Fig. 1.

Of the 13 patients reviewed, seven died, six within two weeks of the onset of the neurological complication. It seems likely that in our Case 1, death, which occurred five months after the onset of the condition, was due to cardiac failure. Those patients who recovered, did so after a period of months and were left with diminished or absent tendon reflexes and minimal weakness. With our limited experience we are not able to draw any conclusions about the efficacy of steroid therapy.

Discussion

The clinical picture presented by these cases can only be adequately accounted for by widespread disease of peripheral nerves or of spinal nerve roots, either alone or in combination. The electromyographic findings, including the demonstration of slowed conduction velocity of motor nerves, supports this view (Simpson, 1958).

The term "Landry-Guillain-Barré syndrome" has limitations which we fully appreciate, but it is a convenient one for the present purpose. Haymaker and Kernohan (1949) reported 50 cases of the Landry-Guillain-Barré syndrome confirmed by necropsy. They showed that many of the classical features of the condition may not appear and pointed out the extreme variability of the C.S.F. changes and the fact that the protein level may rise only very late or not at all.

The appearance of those neurological complications following herpes zoster might be accounted for in different ways. The two conditions could have been entirely unrelated. Secondly, the herpes zoster could have been "symptomatic" in a polyradiculopathy of unknown origin as suggested by Friart and Jeanty (1956) and by Pálffy and Balázs (1958). The sequence of events, the zoster always occurring first, makes both of these possibilities unlikely. The zoster virus could have "activated" a second hypothetical virus. This suggestion was made by Friart and Jeanty (1956) only to be dismissed. "Activation" of one virus by another is an unproven concept, indeed, the reverse, virus "interference", is biologically more probable. The isolation of the virus ECHO 9 from the C.S.F. from one of our cases and of an ECHO 6 virus from the C.S.F. and stools of a patient with the Guillain-Barré syndrome by Parker, Wilt, Dawson, and Stackiw (1960) may be relevant to this point. There is, however, no evidence that these viruses play a significant role in the motor complications of herpes zoster or in the Landry-Guillain-Barré syndrome.

The most likely explanation is that the causal agent in this condition is the zoster virus and that it produces the picture we have described either by spreading within the nervous system or, more likely, by initiating an "allergic" process such as that which is believed to occur in the Landry-Guillain-Barré syndrome and in the demyelinating diseases complicating chickenpox and other exanthemata (Miller and Stanton, 1954). This hypothesis would harmonize best with the long latent period to which we have drawn attention and which also characterizes the rare herpes zoster encephalitis.

Whatever the pathogenesis, it is possible that the cases reviewed here form part of a spectrum at one end of which there are the cases of polyradiculoneuropathy with no cord involvement, at the other cases with severe encephalomyelopathy (McAlpine *et al.*, 1959), our own patient described as Case 3, who had an extensor plantar response, falling into an intermediate group. If our hypothesis is correct the use of steroid drugs in treatment of the motor complications of herpes zoster is rational but it is probable that therapy must be started earlier if it is to be valuable.

Summary

Three cases are presented in which herpes zoster was followed, after a varying interval, by widespread lower motor neurone paresis associated with sensory disturbances and, in two of the three cases, albumino-cytological dissociation in the cerebrospinal fluid. In one case, ECHO virus type 9 was isolated from the C.S.F. Electromyography and nerve conductivity studies indicated peripheral neuropathy.

Ten similar cases have been traced in the literature, and the findings in all 13 cases are reviewed.

The pathogenesis is discussed.

We wish to thank Dr. Murray-Lyon and Dr. Chalmers Davidson for allowing us to study cases under their care.

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THE FEBRUARY (1961) ISSUE

The February (1961) issue contains the following papers:—

Craniopharyngioma in the Elderly. R. W. Ross Russell and J. B. Pennybacker

The Effect of Ageing upon Physiological Tremor. John Marshall

Quadriceps Myopathy Occurring in Middle Age. J. W. Aldren Turner and K. W. G. Heathfield

Origin of Echoes in the Echoencephalogram. Brita Lithander

Cerebral Trauma in Infancy and Intellectual Defect. R. C. Oldfield and Moyra Williams

Observations on Selective Leucotomy. Walpole Lewin

The Size and Growth of the Human Optic Nerve Peter E. Sylvester and Kevser Ari

The Electroencephalogram in Congenital Hypothyroidism: A Study of 10 Cases. Eric A. Nieman

The Electroencephalographic Diagnosis of Manifest and Latent 'Delirium' with Particular Reference to that Complicating Hepatic Cirrhosis. John Laidlaw and A. E. Read

The Rigid Form of Huntington's Disease. A. M. G. Campbell, Beryl Corner, R. M. Norman, and H. Urich

Response of Normal and Multiple Sclerotic Subjects to Typhoid-Paratyphoid Vaccine Injections. E. J. Field, C. A. Green, and Henry Miller

A Huge Osteoma in the Anterior Cranial Fossa. Vl. Hudolin, D. Riessner, S. Kadrnka, and M. Knežević

An Internal Carotid Aneurysm in the Petrous Temporal Bone. Sami Guirguis and Fathy W. Tadros

Chronic Arachnoidal Cysts of the Middle Cranial Fossa and Their Relation to Trauma. P. Tiberin and J. Gruszkiewicz

Proceedings of the Society of British Neurological Surgeons: 62nd Meeting

Book Reviews

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1961, **24**, 173.

HYPERSOMNIA IN DYSTROPHIA MYOTONICA

BY

J. C. PHEMISTER and J. M. SMALL

From the Department of Neurology, The London Hospital

We have been interested to note the occurrence of marked hypersomnia and somnolence in four patients suffering from dystrophia myotonica. Somnolence has been described before in this condition (Rohrer, 1916; Thomasen 1948) but the association has not had much emphasis and cannot be said to be widely known. Three of our patients were known myotonic subjects in whom hypersomnia was a troublesome incidental complaint, but the fourth came complaining of fainting attacks and an unmanageable liability to oversleep, and it was only then that an unrecognized dystrophia myotonica came to light.

Case Reports

Case 1.—M.J., a man aged 30, was an insurance broker. Dystrophia myotonica had been diagnosed 13 years previously. When on holiday fly-fishing, he found an unusual difficulty in striking and a medical acquaintance at the fishing hotel suggested the diagnosis, which was later confirmed by Sir Russell Brain. At this time he already presented a typical picture, with frontal baldness, a myopathic facies, wasting of the sternomastoid muscles, and testicular atrophy. Muscle wasting was general, particularly affecting the forearms and hands.

Family History.—His maternal grandfather had bilateral cataract. His father died in an accident at the age of 59 but had shown no sign of the disorder. An elder brother had early baldness, but no muscle disturbance and no cataract. A younger brother was found to have fairly typical dystrophia myotonica, but had no history of any disturbance of sleep.

Past History.—He had had pneumonia at the age of 12 months and had been "chesty" all his life.

He was given quinidine at first, with moderate improvement. In 1955 he was transferred to procaine amide and responded very well indeed on a dosage of between 4 and 6 g. a day. In January, 1959, he was referred again to Sir Russell Brain with the complaint of increasing lethargy, and was admitted to the London Hospital. His mother, with whom he lived, had become concerned at his periodic liability to sleep on for as long as 48 hours at a time. During a period of several months he might sleep from a Friday evening until the Monday morning. He would be normally rousable, but would resent being wakened and would at once turn over and go back to sleep. His sleep was restless. On the Monday morning he would wake normally and go to work as usual. Apart from this hypersomnia, he was at all times easily apt to go to sleep although he never slept when travelling. He had had no disturbance resembling cataplexy.

On examination, his characteristic myotonic appearance was as described above. He was an intelligent man, alert, and cooperative in conversation. He had a myotonic dysarthria, myotonia of the grip, and myotonia on percussion of the thenar muscles and of the tongue. There was no abnormality of the nervous system apart from the changes to be expected in dystrophia myotonica. There were no abnormal signs in the chest, but the chest expansion was only ¾ in.

The blood picture showed no abnormality. A radiograph of the chest showed bilateral basal bronchiectasis. A radiograph of the skull was normal. An oral glucose tolerance test was normal. Serum sodium and potassium were normal. Radio-active iodine uptake was normal. The 17- ketosteroid and 17-ketogenic steroid excretions were normal, with a normal increase in output after the administration of 60 units of A.C.T.H. twice daily for three days. An electromyogram gave characteristic findings of myotonia.

While he was in bed in the ward, a remarkable immobility of posture was noted. At all times, movement was of restricted excursion so that he had superficially a rather Parkinsonian appearance. He was not drowsy but drifted easily into a light sleep. When the administration of procaine amide was stopped for a time there was a disabling return of the myotonia without evident change in his liability to go off to sleep.

Case 2.—M.C., a woman aged 23, a tailoress, was unmarried. In February, 1959, she began to have fainting attacks. These were liable to occur first thing in the morning when she rose from bed, or when she had been sitting for any length of time in the same position at work. She might have a light-headed feeling without actually losing consciousness, but usually after brief light-headedness she would fall to the ground unconscious without involuntary movement, tongue-biting or incontinence. She would recover consciousness within a matter of minutes and be well apart from slight frontal headache. She knew of no precipitant of the attacks.

For as long as she could remember, she had gone to bed at six o'clock in the evening and slept until it was time to get up to go to work in the morning: she would

have to be shaken awake at seven o'clock. Periodically, she has had spells lasting a few months at a time when she would remain in bed asleep over the entire week-end. "When my mother tried to wake me I would just turn over and go off to sleep again." Her mother described her as being very restless during her sleep.

To direct questioning, she admitted occasional difficulty in releasing her grip when ironing, but she had no complaint referrable to the myotonia.

Family History.—She is the eldest of five sisters, who are all well. The father is well, the mother a migraine subject. There is no family history of epilepsy, muscle disease, or cataract.

Past History.—She had scarlet fever at the age of 11. Recently, a chalazion had been removed from the right lower lid.

On examination, she was a rather poorly cooperative patient of less than average intelligence. She had a myopathic facies with bilateral ptosis, and general muscle wasting and weakness, greater distally. The sternomastoid muscles were only thin straps. There was myotonia of the grip, and on percussion, of the tongue. Tendon responses were all brisk: she had long fingers and a high arched palate, and normal distribution of body hair.

The blood picture was normal, and radiographs of the chest and skull were normal. Serum electrolytes were normal. An electromyogram showed a typical myotonic picture. In the E.E.G. there was no real alpha rhythm, but a mixture of low voltage fast and irregular theta activities diffusely and bilaterally. A little paroxysmal fast activity was present symmetrically in the fronto-temporal regions. Overbreathing produced very little effect. Photic stimulation evoked a good bilateral following response. Ocular compression produced no response.

When in the ward, it was seen that she was always very apt to drop off to sleep though she was easily rousable. She had no episodes of loss of consciousness. She was given procaine amide, 4 g. daily, and with this there was a great subjective improvement and the myotonia disappeared to clinical testing. The somnolence was unaffected.

Case 3.—J.C., a schoolgirl, aged 16, had had difficulty in relaxing her grip since the age of 11. She falls off to sleep very easily, especially when travelling by car or bus, and has always had difficulty in getting up in the morning. She is inclined to sleep always, and never goes to bed later than eight o'clock. Her sister, who sleeps with her, complains of her restlessness at night. She has never had fainting turns, or anything resembling cataplexy. There was nothing relevant in her past history, and her father, mother, and sister are well. There is no family history of muscle disease or cataract.

On examination, there was some wasting of the sternomastoids and of the distal musculature of the upper limbs, and myotonia to percussion of the tongue and of the thenar muscles. She is slightly built and sexually underdeveloped. The nervous system was normal except for dull tendon responses.

The blood picture was normal. Radiographs of the chest and skull were normal. Serum electrolytes were normal. An electromyogram showed the typical changes of myotonia.

Case 4.—J.T., a man aged 38, a clerical worker, at the age of 27 first noticed a nasal quality to his voice. Soon after this, he began to have nasal regurgitation of fluids. His face became thinner and he developed weakness of the hands. Dystrophia myotonica was first diagnosed in 1952. At this time he had a myopathic facies and wasting of the sternomastoid muscles, but no frontal baldness and no testicular atrophy. The weakness increased steadily and his condition was little influenced by quinidine or procaine amide. In May, 1959, he began for the first time to have attacks in which his legs "just gave way". He was found at this time to be taking large doses of methedrine to counter the tendency to go to sleep which had troubled him always. He said that for as long as he could remember he had had a troublesome liability to go off to sleep during the day, and had had to go to bed early and yet be shaken awake in the morning.

Past History.—He had been rejected for the Army at the age of 20 because of "heart trouble".

Family History.—One brother, six years younger, has dystrophia myotonica but not the same tendency to sleepiness. His father and mother, both aged 72, are well. There is no other family history of muscle disease, cataract, epilepsy, or heart disease.

On examination, he was an intelligent, cooperative patient, with a myopathic facies and wasted sternomastoid muscles. He had an indistinct voice with a nasal quality. There was weakness and wasting of the muscles generally but particularly distally in the limbs. Tendon responses were dull in the arms, absent in the legs. No other abnormality was found in the nervous system. He had early bilateral cataracts, typical of dystrophia myotonica, and two chalazions on the right upper eye-lid and one on the left lower lid. Both femoral pulses were impalpable. He had no frontal baldness; the testes were normal.

The blood picture was normal. A radiograph of the chest showed the appearances typical of coarctation of the aorta, and an E.C.G. a PR interval of 0·24 second, and a QRS complex widened to 0·10 second. An electromyogram showed the typical changes of myotonia.

Comment

The similarity in the accounts of the hypersomnia given by the first two patients is striking: both have on occasion slept out the entire week-end. All four have a tendency to fall asleep when their attention is not held, and this might suggest that the disorder is best considered as a narcolepsy. There are a number of points against this. No patient had experienced episodes which could fairly be called cataplectic. None of them described the waves of irresistible sleep to which many narcoleptics are subject: they just went to sleep. Patients with troublesome narcolepsy during the day usually sleep badly at night and wake frequently. These patients, though

admittedly restless, slept soundly. The term narcolepsy is better avoided here, and the condition spoken of as a hypersomnia.

The first patient had been taking quite large doses of procaine amide when the disturbance of sleep first appeared, and it was questioned whether the drug might be a cause. However, neither drowsiness nor a tendency to sleep have been reported after its use, and on the contrary it is liable to cause insomnia. Later, similar hypersomnia was noted in patients who had never received the drug.

The apathy and lack of interest shown by these patients was very marked, and it was difficult not to feel that the tendency to go off to sleep was associated with their very immobility. However, such a picture is common enough in myotonic patients who have no disturbance of sleep whatsoever. In all four patients the restlessness of their sleep at night was in striking contrast to the vegetative way in which they spent their days, and did not suggest that the excessive sleep was due to any of the accepted endocrine deficiencies. Closely questioned on the matter, the first patient said that his periods of oversleeping occurred usually in the colder weather, while the second patient was more inclined to associate hers with the summer.

The real point of interest lies in whether this hypersomnia is due to a primary disturbance of the part of the central nervous system concerned with sleep, or whether it is in some way secondary to the myotonic state. Curious narcoleptic states, and disturbances of sleep are not uncommon in severe myopathies where there is gross affection of the respiratory musculature. They have been attributed to slowly developing biochemical changes consequent upon the chronic failure of lung ventilation. Such a mechanism, even if true of some myopathies, clearly does not obtain here, for all four patients had been known to be unusually prone to sleepiness since early childhood and certainly before any weakness was apparent. Another bare possibility, suggested by the patients' immobility in bed, that the myotonia gripped them and held them still so that like Pavlov's confined dog they went to sleep, may be discounted because of the restlessness of their sleep.

The likelihood seems to be, considering the histories of the four patients with their resemblances and their accounts of sleepiness going back to childhood, that the disturbance is due to some innate change in the central nervous system. It is yet another of the extramuscular disturbances to be found in this curious disease.

Summary

Four patients are reported in whom somnolence and hypersomnia were associated with dystrophia myotonica.

We are grateful to Sir Russell Brain, Dr. P. H. Sandifer, and R. A. Henson for permission to describe cases under their care.

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THE FICTION OF THE "GERSTMANN SYNDROME"

BY

ARTHUR L. BENTON

From the Departments of Neurology and Psychology, University of Iowa, Iowa City, Iowa, U.S.A.

The problem with which this study is concerned can be stated as follows. A patient with parieto-occipital disease may show one or more of a relatively large number of diverse behavioural deficits. When he presents with two, three, or more of these symptoms, the latter may be viewed by the clinical observer as forming a naturally occurring combination of deficits and given the status of a syndrome, this status implying that the concurrence of deficits is not a chance one, that there is an underlying factor responsible for it, and that it possesses a distinctive neuropathological significance. Once such a special combination or syndrome is established, not only is it used in the observation and description of subsequent cases but it may also determine which aspects of a patient's behaviour are selected for study and which are not. The "Gerstmann syndrome" represents such a combination of behavioural deficits. The study to be reported examines the question of whether, as is usually assumed, this "assembly of unlikely and unexpected symptoms" (Critchley, 1953) is a naturally occurring combination or whether it is only one of a very large number of more or less fortuitous combinations of behavioural deficits which may be encountered in patients with cerebral disease.

The history of the Gerstmann syndrome has been recounted in detail elsewhere (cf. Critchley, 1953; Benton, 1959); only a few major points need be mentioned to introduce the present investigation. Before the end of the nineteenth century, the four behavioural deficits comprising the syndrome—right-left disorientation, acalculia, agraphia, and finger agnosia—had been described as occurring in patients with cerebral disease. The first three were well-known symptoms but the description of finger agnosia in 1888 by Jules Badal had escaped the attention of neurologists, a fact which is not altogether surprising in view of the circumstances that the Bordeaux eye specialist published in an ophthalmological journal, and the finger agnosia which he quite clearly described was only one of a large number of deficits shown by his patient. In 1924, Gerstmann once again described finger agnosia, designating it as "a circumscribed disorder of orientation to one's own body". In 1927, he advanced the idea that finger agnosia and agraphia formed "a new syndrome". However, in 1930 he enlarged the syndrome to include right-left disorientation and acalculia and proposed that it had a highly specific neuropathological significance. At the same time, he discussed the question of the *Grundstörung* responsible for this presumably "natural" concurrence of behavioural deficits.

Clinical experience appeared to confirm the real existence of the syndrome; case reports of patients manifesting it appeared in the literature and speculations regarding the basic impairment underlying its occurrence were offered. However, it was certainly not rare to encounter patients who showed one, two, or three deficits but not the full syndrome. While such observations were often interpreted as simply representing *formes frustes* of the syndrome, they did indicate at least that the four symptoms did not necessarily occur together in every case and they did have implications regarding the cogency of those theoretical formulations which had been advanced to account for an obligatory concurrence of the deficits. On the other hand, a wide variety of other deficits were also observed to occur in connexion with any or all of the four symptoms. These were given a subordinate status as accompanying symptoms which might or might not be manifested. Among them were general mental impairment, aphasic disorders, colour agnosia, visual disorientation, dyslexia, and constructional apraxia. Indeed, the last-named deficit, constructional apraxia, has been observed so often to accompany one or more of the four deficits that some authors have come to consider it, explicitly or implicitly, as part of the syndrome. For example, Ajuriaguerra and Hécaen (1960), discussing the interrelations of the elements of the syndrome and the connexions with other symptoms, remark that "the most frequent and most important association is that between finger agnosia and constructional apraxia. We have seen that such an association cannot be considered to be simply fortuitous or anatomically conditioned".

If the "Gerstmann syndrome" is a naturally occurring combination of interrelated deficits, all of which are expressions of a single basic impairment, and not merely the product of selective attention and observation, the four behavioural deficits which comprise it should show stronger "associative bonds", so to speak, among themselves than they do with symptoms which are considered to be outside of the syndrome. If unbiased analysis should show this to be the case, the findings could be reasonably interpreted as evidence for a special coherence of the four symptoms and both the designation of the combination as a syndrome and a search for the common factor responsible for the coherence are justified. On the other hand, if such analysis should disclose that this is not the case, the findings could be reasonably interpreted as indicating that this particular combination of deficits is no more or less likely to occur in patients with cerebral disease than a great many similar combinations and that, unless it can be shown to have a distinctive neuropathological significance, neither its designation as a syndrome nor the postulation of a common psychoneurological factor to account for it (as distinguished from other combinations) is justified.

It might be thought that a comprehensive survey of the pertinent clinical literature would provide the answer to this question of the phenomenological reality of the Gerstmann syndrome. However, the literature proves to be virtually without value in this respect. The methods and criteria utilized for making clinical judgments regarding the presence or absence of defect in the performances investigated are so diverse that the findings from one case to another are not comparable. Not infrequently the criteria employed in making judgments of deficit are not mentioned and notations such as "slight finger agnosia", "questionable right-left disorientation", or "no noteworthy constructional apraxia" are made. Moreover, the majority of case reports fail to mention the presence or absence of one or more pertinent accompanying deficits and hence must be excluded from a systematic analysis. Finally, the factor of selective attention and observation when one is dealing with an already established entity, such as the Gerstmann syndrome, may introduce a bias in the original observations for which the reviewer cannot correct.

It seems evident that the question of the status of the Gerstmann syndrome as a behavioural phenomenon can be answered only by an investigation which has been deliberately designed to answer it and which employs explicitly described procedures for assessment and criteria for judgment. The present paper reports such an investigation.

Case Material and Methods

The case material consisted of 100 non-psychotic patients with unequivocal diagnoses of disease or injury involving the cerebral hemispheres who had been seen in the neurological and neurosurgical services of the University Hospitals and Veterans Administration Hospital, Iowa City. Any patient who was suffering from acute illness, whose behavour raised the question of psychosis, who had a history of treatment in hospital for a psychiatric disorder, or whose history was suggestive of a state of mental defect dating back to childhood, was excluded from the study. All the patients were between the ages of 16 and 64 years and were clearly capable of understanding directions, cooperating in the test procedures and undergoing one to two hours of examination without discomfort. The mean age of the group was 42 years. The mean educational level was 10 years (range: 5 to 16 years). A variety of cerebral conditions, focal and diffuse, was represented in the group. The performances of 12 right-handed patients with focal disease involving the left parietal lobe were analysed separately, in addition to the main analyses of the total group of 100 patients of which they formed a part.

A control group of 100 non-psychotic patients from the neurological, neurosurgical, and medical services who showed no evidence or history of cerebral disease or injury were also examined, their performances being utilized to establish objective normative standards on the basis of which the presence or absence of impairment could be defined. The mean age of this group was 41 years (range: 16 to 65 years) and mean educational level was 10 years (range: 5 to 14 years).

All the patients were given a battery of seven tests designed to provide objective and comprehensive assessments of the following capacities: (1) right-left orientation; (2) finger localization; (3) arithmetic calculation; (4) writing; (5) constructional praxis; (6) reading; (7) visual memory. The testing procedures were as follows:

Right-left Orientation.—This test battery (32 items) required the patient to execute localizing movements to oral command and assessed the following aspects of right-left orientation: (A) with the aid of vision, identification of single lateral body parts on one's own body; (B) with the aid of vision, execution of double uncrossed and crossed commands with respect to lateral body parts on one's own body, *e.g.*, left hand on right eye; (C) without the aid of vision, identification of single lateral body parts; (D) without the aid of vision, execution of double commands; (E) identification of single lateral body parts on a front-view representation of a man; (F) execution of double commands involving identification of lateral body parts of both the patient and the representation, *e.g.*, patient's right hand on a man's right eye. The details of this test battery may be found in a paper by Benton and Kemble (1960). Level of performance was defined as the number of correct localizations made by the patient.

Finger Localization.—This test battery (80 items) assessed the following aspects of finger identification: (A) with the aid of vision, presentation of single fingers

on oral command; (B) identification of single fingers on schematic drawings of the hands; (C) with the aid of vision, identification of single fingers which had been touched; (D) without the aid of vision, identification of single fingers which had been touched; (E) without the aid of vision, identification of pairs of fingers subjected to simultaneous tactile stimulation. (For details regarding the arrangements for tactile stimulation of the fingers, see Benton, 1959.) Level of performance was defined as the number of correct localizations made by the patient.

Arithmetic Calculation.—This untimed 16-item written test consisted of simple problems in addition, subtraction, multiplication, and division involving one- and two-digit numbers. Level of performance was defined as the number of correct solutions.

Writing.—The patient was asked to write his name, copy two simple sentences, write two simple sentences to dictation, and write down anything that came into his mind. Unlined $5\frac{1}{2} \times 8$ in. paper was used. Each specimen of writing was independently rated by two examiners on the basis of the following factors: alignment of lines; elisions and omissions; formation of letters; spelling; substitutions and additions. Each of these factors was rated from 0 (poor) to 2 (within normal limits). Level of performance was defined in terms of an overall rating consisting of the sum of the two examiners' ratings on each of these factors. However, in the case of patients with sensorimotor deficits of the preferred hand, the "formation of letters" factor was excluded from consideration, and a weighted sum of the examiners' ratings on the other factors was computed.

Constructional Praxis.—Both two-dimensional and three-dimensional praxis was assessed. The two-dimensional task consisted in having the patient copy six "stick" designs presented by the examiner while the three-dimensional task consisted in having him copy four models made of rectangular blocks of various sizes and dimensions. The patient was allowed to use only one hand in arranging the sticks or blocks. Level of performance was defined as the number of sticks and blocks correctly placed.

Reading.—The patient read four short paragraphs and, with the paragraphs in view, answered questions which assessed his understanding of them. Level of performance was defined as the number of questions correctly answered. No time limit was enforced.

Visual Memory.—Multiple choice form G of the visual retention test (Benton, 1953) consisting of 15 designs was used. Each design was presented to the patient for 5 sec., after which he was required to identify the design on a card containing it and three similar designs. Level of performance was defined as the number of correct choices made by the patient.

Distributions of the scores of the 100 control patients on each of the seven tests were made and inspected. For each distribution, a score which was equalled or exceeded by 91 to 94% of the patient's was selected as a "cutting score" and scores below this level were considered to indicate significantly defective performance. Natural "breaks" which occurred in the lower ends of some of the distributions were utilized in establishing these cutting scores, a circumstance which accounts for the slight variation in the percentage values of the various scores.

The Investigation

Relationships among Performances.—The intercorrelations among the seven performances for the total group of 100 brain-damaged patients are shown in Table I. These are "second-order" correlation coefficients, from which the effects of variation in age and educational level on performance have been eliminated. Inspection of this matrix suggests that the correlations among the elements of the syndrome are neither higher nor lower than those between these elements and the performances which presumably do not belong to the syndrome. Thus, while the highest correlation coefficient in the matrix (0·62) is between two syndrome performances (right-left orientation vs. finger localization), it will be seen that the lowest correlation coefficient (0·35) is also between two syndrome performances (finger localization vs. calculation). The mean correlation coefficient of the performances within the syndrome (derived from averaging the six relevant correlation coefficients) is 0·48. This may be compared with the mean correlation coefficient between the syndrome performances and those performances which are outside of the syndrome. This statistic (derived from averaging the 12 relevant correlation coefficients) is 0·52, indicating that the syndrome performances show no closer relationship among themselves than

TABLE I

SECOND-ORDER CORRELATION COEFFICIENTS (AGE AND EDUCATION "PARTIALLED OUT") IN 100 BRAIN-DAMAGED PATIENTS

	Finger Localization	Writing	Calculation	Constructional Praxis	Reading	Visual Memory
Right-left	0·62	0·48	0·46	0·51	0·48	0·57
Finger localization		0·52	0·35	0·60	0·42	0·50
Writing			0·46	0·44	0·57	0·52
Calculation				0·51	0·60	0·58
Constructional praxis					0·42	0·47
Reading						0·56

TABLE II

MEAN CORRELATION COEFFICIENTS BETWEEN INDIVIDUAL PERFORMANCES AND THE SYNDROME IN 100 BRAIN-DAMAGED PATIENTS

	r
Right-left vs. finger localization – writing – calculation	0·52
Finger localization vs. right-left – writing – calculation	0·51
Writing vs. right-left – finger localization – calculation	0·49
Calculation vs. right-left – finger localization – writing	0·42
Constructional praxis vs. right-left – finger localization – writing – calculation	0·52
Reading vs. right-left – finger localization – writing – calculation	0·52
Visual memory vs. right-left – finger localization – writing – calculation	0·54

they do with performances outside of the syndrome.

A more detailed analysis of the strength of the relationships existing among elements of the syndrome as compared with that existing between them and the other performances is presented in Table II, which shows the mean correlation coefficient of each syndrome performance with the other three syndrome performances and of each extra-syndrome performance with the four syndrome performances. The findings indicate quite clearly that constructional praxis, reading, and visual memory are as closely related to the elements of the syndrome as the latter are among themselves, *i.e.*, that the elements of the syndrome do not show particularly close associative bonds.

Cohesiveness of Syndromes.—As has already been noted, the mean intercorrelation among the elements of the syndrome is 0·48, which may be interpreted as an index of its "cohesiveness", *i.e.*, of the tendency of elements to vary concurrently. Thirty-five combinations of four performances each can be formed from the seven "parietal" performances investigated in this study. Each combination will include one or more elements of the syndrome, one of them being the syndrome. If there is a special tendency for the elements of the syndrome to vary concurrently, its observed mean intercorrelation of 0·48 should be higher than those derived from combinations consisting of mixtures of syndrome and non-syndrome elements. The mean correlation coefficient (derived from the six relevant correlation coefficients) of each of the 34 mixed combinations was computed. They ranged in size from 0·48 to 0·54. Two coefficients were as high as 0·54 and four were as low as 0·48. It is clear from these findings that all 35 combinations of elements show about the same degree of cohesiveness and that the syndrome is not at all distinctive in this respect.

The incidence of significant deficit in performance (as defined above, *i.e.*, performances which fell within the lowest 6 to 9% of the scores of the control group) was computed for each patient. Twenty-nine showed no significant deficits and 23 showed only one deficit. The remaining 48 patients showed two to seven deficits, 10 of them showing four deficits. Examination of these 10 sets of four deficits disclosed that all involved combinations of syndrome and non-syndrome performances. The pure Gerstmann syndrome did not appear. The combination of deficits in finger localization, writing, reading, and constructional praxis appeared twice. Eight other combinations appeared once. Again the findings indicate no particularly strong tendency for the symptoms of the Gerstmann syndrome to appear concurrently.

Performances of Patients with Left Parietal Lesions.—It might be argued that assumptions about the essential unity of the elements of the Gerstmann syndrome hold only for patients with parieto-occipital disease of the dominant hemisphere and that a study involving patients with various types of lesion cannot provide cogent evidence about these assumptions. This contention is quite debatable. The explanations which have been advanced to account for the supposedly obligatory concurrence of the symptoms have been of a broad psychological or psychoneurological nature and have no necessary reference to a specific locus of the responsible lesion. Thus such concepts as the importance of intact finger gnosis for writing and calculation, of intact right-left orientation for calculation, or of intact spatial thinking for all the performances have been applied to all situations in which the deficits appear, *e.g.*, developmental deficit, and are not dependent upon the presence of a specified lesion. Nevertheless, it seemed worthwhile to make a separate analysis of the performances of the 12 right-handed patients in the group who had disease of the left parietal lobe to determine the nature of the relationships of the syndrome performances among themselves and with the other performances.

The mean correlation coefficient of each of the syndrome performances with the other three syndrome performances and of each extra-syndrome performance with the four syndrome performances is shown in Table III. It is evident from inspection of this table that constructional praxis, reading, and visual memory are as closely related to the elements

TABLE III

MEAN CORRELATIONS BETWEEN INDIVIDUAL PERFORMANCES AND THE SYNDROME IN 12 PATIENTS WITH LEFT PARIETAL LOBE DISEASE

	r
Right-left vs. finger localization – writing – calculation	0·53
Finger localization vs. right-left – writing – calculation	0·38
Writing vs. right-left – finger localization – calculation	0·21
Calculation vs. right-left – finger localization – writing	0·51
Constructional praxis vs. right-left – finger localization – writing – calculation	0·53
Reading vs. right-left – finger localization – writing – calculation	0·61
Visual memory vs. right-left – finger localization – writing – calculation	0·44

of the syndrome as the latter are to each other. Thus in this group of patients with focal disease of the left parietal lobe there is also no evidence that the elements of the syndrome show any noteworthy strength of association.

The significant deficits in performance shown by these 12 patients are shown in detail in Table IV. It will be seen that no patient showed the full Gerstmann syndrome. Four patients (E.H., R.K., A.P., D.T.) presented with three Gerstmann symptoms but in each case these appeared in association with other deficits.

Discussion

This investigation represents an attempt to determine whether the four behavioural deficits comprising the so-called "Gerstmann syndrome" form a distinctive constellation. A variety of analyses, which provided evidence concerning the strength of the relationships existing among these elements and that existing between the elements and performances which do not belong to the syndrome, were done. These analyses, made both on a large group of patients with diverse types of cerebral disease and a smaller group of right-handed patients with focal disease of the left parietal lobe, consistently indicated that the particular combination of behavioural deficits which form the syndrome show no stronger internal associative bonds than do a score of other combinations of behavioural deficits. A large number of combinations of four behavioural deficits may be presented by patients with cerebral disease. The analyses of the present study suggest that there is about an equal probability of occurrence for any one of them, including the combination known as the Gerstmann syndrome.

These results provide a reasonable explanation of the frequent reports in the clinical literature of so-called incomplete forms of the syndrome as well as the even more frequent reports of symptoms which are observed to "accompany" it. Such behavioural pictures are simply other combinations of deficits which tend not to be accepted in their own right because of the predilection of clinical observers to look first for elements of the Gerstmann combination and to use these elements as an anchoring point to which accompanying symptoms may be attached. The findings also indicate that theoretical speculations concerning the basic impairment which must underlie the so-called Gerstmann syndrome are hardly warranted. There is no obligatory concurrence of deficits to account for and, in any case, if it is necessary to explain this particular combination of deficits, it is equally necessary to explain the existence of a score of other combinations of behavioural deficits.

A tenable conclusion from these results is that, judged from the standpoint of behavioural analysis, the Gerstmann syndrome is a fiction; it is simply an artifact of defective and biased observations. Objec-

TABLE IV

INCIDENCE OF DEFICITS IN PATIENTS WITH LEFT PARIETAL LOBE DISEASE

No.	Patient	Right-left	Finger Localization	Writing	Calculation	Constructional Praxis	Reading	Visual Memory
1	N.F.	o	o	o	o	+	o	+
2	E.H.	+	+	o	+	+	o	+
3	V.H.	o	o	o	o	o	o	o
4	R.K.	+	+	o	+	+	+	+
5	E.K.	o	o	o	o	+	o	o
6	A.P.	+	+	o	+	+	+	o
7	D.T.	+	o	+	+	o	+	o
8	E.H.	o	o	o	o	o	o	o
9	R.M.	o	o	o	o	o	o	o
10	E.M.	o	o	o	o	o	o	o
11	J.C.	+	+	o	o	+	o	o
12	J.D.	o	o	o	o	o	o	o

(+ = Deficit; o = no deficit)

tive, unbiased observation discloses a large number of combinations of parietal deficits. Since all these combinations appear to be about equally strong with respect to their internal associative bonds and frequency of occurrence, either all or none should be designated as syndromes.

This study has not been concerned directly with the question of the possible neuropathological significance of the combination of deficits known as the Gerstmann syndrome. Despite the fact that this combination of deficits does not seem to be any different from many other combinations of parietal symptoms, there is the possibility that when it is manifested in pure form it does possess the highly specific focal diagnostic significance which has been claimed for it, namely, a lesion of "that nodal area which corresponds to the angular gyrus in its transition to the second occipital convolution" (Gerstmann, 1957). However, Critchley (1953), reviewing the clinical literature, was inclined to conclude that the syndrome was more reasonably interpreted as a sign of parietal disease in general rather than specifically indicating a lesion of the angular gyrus. Similarly, Heimberger, DeMyer, and Reitan (1957) found that when patients manifested the full syndrome, the responsible lesion, even when restricted to the dominant hemisphere, was invariably an extensive one. Finally, there are case reports, such as the recent one by Brusa, Rossi, and Tartarini (1960), of the occurrence of the syndrome in patients with lesions apparently restricted to the frontal lobes. Thus those analyses of the question as have been done throw considerable doubt on the assertion that the syndrome has a highly specific focal diagnostic import. If it does possess such a significance, it might be expected that the other 34 of the 35 syndromes investigated in this study would also have a similarly specific significance. But the weight of clinicopathological evidence gathered over the last 60 years makes it extremely unlikely that such "punctate" localization of functions or deficits exists.

In directing the attention of neurologists both to certain disorders of the body schema and to the unusual variety of combinations of behavioural deficits which a brain-damaged patient may show, the Gerstmann syndrome has perhaps been a useful fiction during the past 30 years. Now that these purposes have been accomplished, adherence to the fiction may well operate to retard further advances in the understanding of the patterns of behavioural deficit which may occur as a consequence of cerebral disease, for it tends to prejudice clinical observation and to produce a distorted picture of the organization of abilities and disabilities in brain-damaged patients.

Summary

Systematic, objective analysis of the performances of patients with cerebral disease on seven "parietal" tasks (right-left orientation, finger localization, writing, calculation, constructional praxis, reading, visual memory) indicates that many combinations of deficits, including that known as the "Gerstmann syndrome", may be observed. The syndrome appears to be no different from the other combinations in respect to either the strength of the mutual interrelationships among its elements or the strength of the relationships between its elements and performances not belonging to it. These results hold both for patients with diverse cerebral conditions and for those with focal lesions of the dominant parietal lobe.

The findings are interpreted as indicating that the Gerstmann syndrome is an artifact of defective and biased observation. Further, a review of the pertinent clinical literature offers little support for its alleged focal diagnostic significance. The general conclusion is that the syndrome is a fiction which has perhaps served a useful purpose in the past in certain respects, but which now carries the hazard of retarding advances in the understanding of the organization of abilities and disabilities in patients with cerebral disease.

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VINYON "N" AS DURAL SUBSTITUTE AND ITS USE IN OTHER NEUROSURGICAL CONDITIONS

BY

PAUL TENG

From the Neurosurgical Service, Kaiser Foundation Hospital, Los Angeles, California

The search for a material to be utilized as dural substitute has been a continuous one for the last six decades. Many materials have been tried, including the different metals, various biological tissues, and plant derivatives. Recently, synthetic products have been utilized as dural substitute. Among these, Vinyon "N" (Teng and Feigin, 1955), Teflon (Teng, unpublished data), and Orlon* (Huertas, 1955) have shown the most promising results, producing only minimal tissue reaction when buried intracranially in experimental animals.

Since publication of the results obtained in experimental monkeys, Vinyon "N" has been used in 40 clinical cases with various neurosurgical conditions, which included its use as (1) dural substitute in repairs of dural defects produced by surgery, trauma, or tumour; (2) bone lining, in the prevention of bone reunion in craniostenosis; and (3) nerve wrap after neurolysis in cicatrization (Table I).

TABLE I

VINYON "N" USED IN VARIOUS NEUROSURGICAL CONDITIONS

Cerebral Dural Defects	
Glioma	13
Meningioma	4
Astrocytoma	1
Haemangioma	1
Vascular anomaly	1
Cortical laceration, open wound	1
Cerebrospinal fluid rhinorrhoea	1
Subtemporal decompression	4
Cerebellar Dural Defects	
Astrocytoma	2
Spinal Dural Defects	
Tumour	2
Trauma	2
Peripheral Nerve Wrap after Neurolysis	2
Craniostenosis	6
Total	40

Vinyon "N" Cloth

The Vinyon "N" used in these experiments, is a synthetic fabric woven into cloth, constructed of 144 wrap threads and 90 filling yarns per square inch. The pattern weave, consistency, and colour are those of China silk. It can readily and repeatedly be sterilized in boiling water without any appreciable damage. Autoclaving stiffens it.

Clinical Observations

From February, 1956, to July, 1960, Vinyon "N" cloth has been used in 40 neurosurgical cases. In 32 instances it was used as dural substitute. These included 26 cerebral dural defects, two cerebellar dural defects, and four spinal dural defects. In six infants it has been utilized as bone lining after a "grooving" craniectomy for craniostenosis. It has also been used in two patients as nerve wrap, in a sciatic trunk and a radial nerve, after neuroloysis in severe cicatrization. The duration of observation in these 40 cases varied from four to 52½ months (Table II).

As Cerebral Dura Substitute.—Vinyon "N" cloth has been used to cover cerebral dural defects in 26 clinical cases, which included 13 malignant gliomas, four meningiomas, four subtemporal decompressions, and one case each of astrocytoma, cerebrospinal fluid rhinorrhoea, cortical laceration, vascular anomaly, and haemangioma (Table I). In each instance, the Vinyon "N" cloth was tucked under the edge of the dura (Fig. 1B). The technique used in applying Vinyon "N" cloth as a dural substitute has been described in detail in a previous paper on animal experiments (Teng and Feigin, 1955). Meningocerebral adhesions frequently developed along the suture line in edge-to-edge anastomosis (dura to Vinyon "N"), but no such adhesions occurred in eversion suturing or when tucking the edge of dural substitute under the edge of dura mater. This technique has been followed in all cases of this series.

In 15 cases, it was possible to recover the Vinyon "N" cloth from the site of surgery. These included 13 cases of malignant glioma at necropsy, and in

*The Vinyon "N" cloth used in this study was supplied by the Carbido and Carbon Chemical Company, New York.

TABLE II

VINYON "N" CLOTH RESIDENT IN TISSUE

Case No.	Manner of Utilization	Diagnosis and Site of Vinyon "N" Used	Date of Operation	Approximate Duration to July 1, 1960 (mth.)
1	Substitute for cerebral dura	Left parieto-occipital astrocytoma	6/3/58	25
2	" " " "	Left temporal lobe haemangioma	1/23/57	41
3	" " " "	Left frontal meningioma	8/6/56	47
4	" " " "	Left frontal parasagittal meningioma	5/26/56	49
5	" " " "	" " " "	11/14/57	31½
6	" " " "	Right frontal parasagittal meningioma	8/14/57	34½
7	" " " "	Left parietal vascular anomaly	5/14/16	49½
8	" " " "	Right temporoparietal laceration	10/5/56	45
9	" " " "	Right subtemporal decompression	8/15/56	46½
10	" " " "	" " "	8/21/56	46½
11	" " " "	Left subtemporal decompression	11/17/56	43½
12	" " " "	" " "	12/29/57	30
13	" " " "	Frontal base, cerebrospinal fluid rhinorrhoea	5/3/57	38
14	Substitute for cerebellar dura	Right cerebellar astrocytoma	2/29/56	52
15	" " " "	" " "	6/5/59	13
16	Substitute for spinal dura "	D_2 to D_3 meningioma	11/19/58	19½
17	" " " "	C_2 to C_5 intramedullary hemangioma	4/19/57	38½
18	" " " "	Cauda equina, compression fracture	11/20/57	31½
19	" " " "	" " " "	6/10/57	36½
20	Bone lining, in craniostenosis	Premature closure, sagittal and frontal sutures	2/15/56	52½
21	" " " "	Premature closure, sagittal suture	3/4/56	52
22	" " " "	" " " "	5/6/57	38
23	" " " "	" " " "	9/1/59	10
24	" " " "	" " " "	9/12/59	9½
25	" " " "	" " " "	9/17/59	9½
26	Peripheral nerve wrap "	Cicatrization, left radial nerve, upper arm	4/9/57	38½
27	" " "	Cicatrization, right sciatic nerve	4/29/59	14

two instances it was recovered from patients undergoing subsequent surgery. In the 13 necropsied cases, the length of time that the Vinyon "N" cloth had been buried in tissue ranged from four to 22 months. In the others, one a case of frontal meningioma and the other a subtemporal decompression, the cloth was removed, in part, for microscopic examination, after being examined *in situ*. In these two, the dural substitute had been used to cover the dural defect for periods of 34 and 30 months, respectively. None of the 27 patients currently alive reveal any clinical evidence of irritative effect from the synthetic fabric up to the time of writing.

In all of the 15 cases mentioned above, the dural substitute was easily reflected or removed, with or without gentle blunt dissection, as necessary, there being no adhesions at the site of the cerebral wound. Here and there were scattered fine strands of fibrous tissue adherent to cortical vessels, where dissection was needed to lift the dural substitute from the cortex without tearing the pia mater. As a rule, dense scar tissue was found on the outer surface of the dural substitute, but on its under surface there was a thin layer of transparent, glistening membrane, the thickness of an opaque arachnoidea. No connective tissue capsule was found to enclose the dural substitute in any of the 15 cases. Microscopic examination showed the dural substitute to be infiltrated by a few lymphocytes and foreign body giant cells. Minimal proliferation of the arachnoid cells was noted. The underlying cortex appeared normal. There was no adhesion between the dural substitute and the surgical wound in the cerebrum.

The following case is illustrative:—

This 30-year-old man was operated on on August 6, 1956 (Table II, Case 3). A large meningioma, *en plaque*, was removed through a left frontal craniotomy. Both the bone flap and the dura were discarded because of tumour infiltration. The frontal bone measured 1·5 in. in thickness. Hyperosteosis extended to the left supra-orbital plate and the ocular globe was displaced downward. A piece of Vinyon "N" cloth, 3 × 3 in. in diameter, was used to cover the dural defect.

Two years and 10 months later he was again operated upon for removal of the remaining portion of left frontal bone, supra-orbital rim and plate, and the nasal bone. The frontal wall of the cranium and the orbital rim were reconstructed with grafted ilium. At surgery, the Vinyon "N" cloth was examined. Dense fibrous tissue was found on the outer surface of the dural substitute, but its under surface was covered only by a thin layer of fibrous strands which were not adherent to the underlying cortex. In places, the dural substitute was loosely anchored to the cortical vessels by thin strands of connective tissue which were easily separated by dissection, without tearing the pia membrane and cortex. In one small area, where the cortex was not covered with dural substitute, dense scar tissue was found, extending from the epidural region to the cerebral cortex, with abundant traversing vessels.

A small piece of Vinyon "N" cloth, excised for microscopic examination, showed scattered lymphocytes and foreign body giant cells lodged among the meshes of the

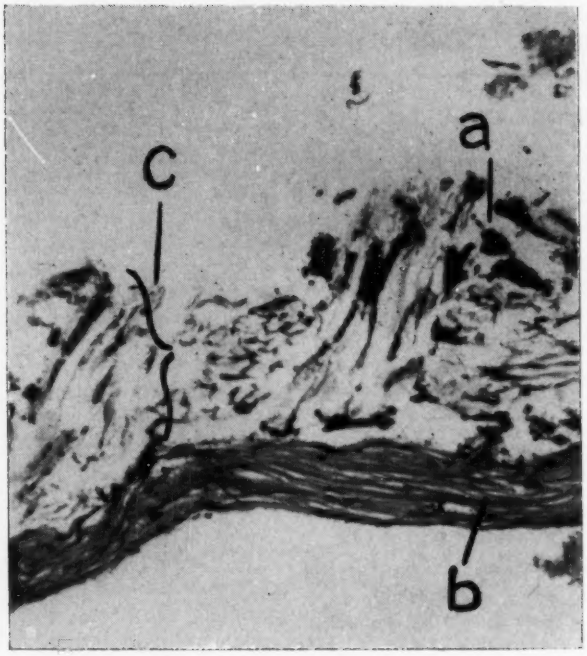

FIG. 2.—Section of dural substitute, Vinyon "N", removed 34 months later. × 80. (a) large foreign body giant cells; (b) thin layer of fibrous tissue lining under surface; (c) total thickness of silk-like Vinyon "N" cloth.

dural substitute, and a thin layer of connective tissue on its under surface (Fig. 2).

Despite the fine pores of the Vinyon "N" cloth, it has been used to repair rhinorrhoea of the cerebrospinal fluid. The following is an illustration of an extreme case of cranionasal fistula.

A 27-year-old man (Table II, Case 13) was admitted to the hospital on May 1, 1957, because of cerebrospinal fluid leaking through the nose for two years, after a motorcycle accident. He had survived five episodes of septic meningitis in the past two years. Surgical repair of the fistula had been recommended at another hospital, but this was refused. On May 3, 1957, a right frontal craniotomy was performed, and a large bone and dural defect, 1·5 cm. in diameter, was found in the cribriform plate. Granulations in the fistula were curetted, then packed with gelfoam soaked with bacitracin and polymyxin solution. A small piece of Vinyon "N" cloth was laid on the inner surface of the dural defect. The postoperative course was uneventful, and no cerebrospinal fluid has leaked since surgery.

As Cerebellar Dural Substitute.—In two cases of cerebellar astrocytoma, after removal of the tumour, the dura was not resutured but the cerebellum was covered with a piece of Vinyon "N" cloth, placed in a position similar to that used to cover the cerebrum. Neither of the patients, after 13 and 52 months respectively, show any ill effects since its placement in the posterior fossa.

As Spinal Dural Substitute.—Vinyon "N" has been used to cover spinal dural defects in four cases. In three instances it was placed after decompression of the spinal cord or cauda equina. Compression was caused by trauma in two of the cases, and tumour in the other. In the two patients with compression of the cauda equina caused by a compression fracture of the upper lumbar spine, the roots of the cauda equina were markedly congested and swollen. The dura was left open for the purpose of decompression, and a strip of Vinyon "N" cloth was placed to cover the dural defect. The dural defect in the third patient was produced by excision of a meningioma. In all three cases the dural substitute has been in place for periods ranging from 19⅓ to 36⅓ months, and none have demonstrated any irritative effect.

One case of spinal dural substitute is illustrated below:

This 36-year-old male school teacher (Table II, Case 17) went to surgery on April 19, 1957, where a C_2 to C_5 laminectomy was performed, and a large intramedullary haemangioma was found. Excision of the tumour was deemed infeasible. The cervical cord was hugely distended by tumour, its width measuring approximately 1·5 in. The tumour extended from C_2 to C_5. Multiple posterior incisions were made in the distended cord, and the dura left open for the purpose of decompression. A piece of dural substitute, 1 × 4 in., was sutured to the dura to cover the exposed section.

Before exploration, the patient was quadriplegic. After surgery, he regained the limited use of both upper limbs. Up to the time of writing, he is able to feed himself and can roll his own wheelchair. The Vinyon "N" material, buried in the spinal canal for 38⅓ months, has not produced any untoward effect.

As Nerve Wrap in Cicatrization.—One of the aims of neurolysis is to prevent recurrence of compression by regrowth of scar tissue along the course of the dissected nerve. It has often been a problem to find a healthy soft tissue bed for transplantation of the nerve after neurolysis, in cases of severe and extensive cicatrization. In this series, two cases of cicatrization of a major nerve trunk, one a sciatic nerve and the other a radial nerve, were treated with neurolysis and wrapping with Vinyon "N" cloth. The purpose of using a nerve wrap in these cases was to prevent scar tissue infiltration of the nerve.

The case of cicatrization of the sciatic nerve is illustrated in the following:

A 36-year-old man (Table II, Case 27) was injured in World War II (1944) by a shell wound in the right posterior

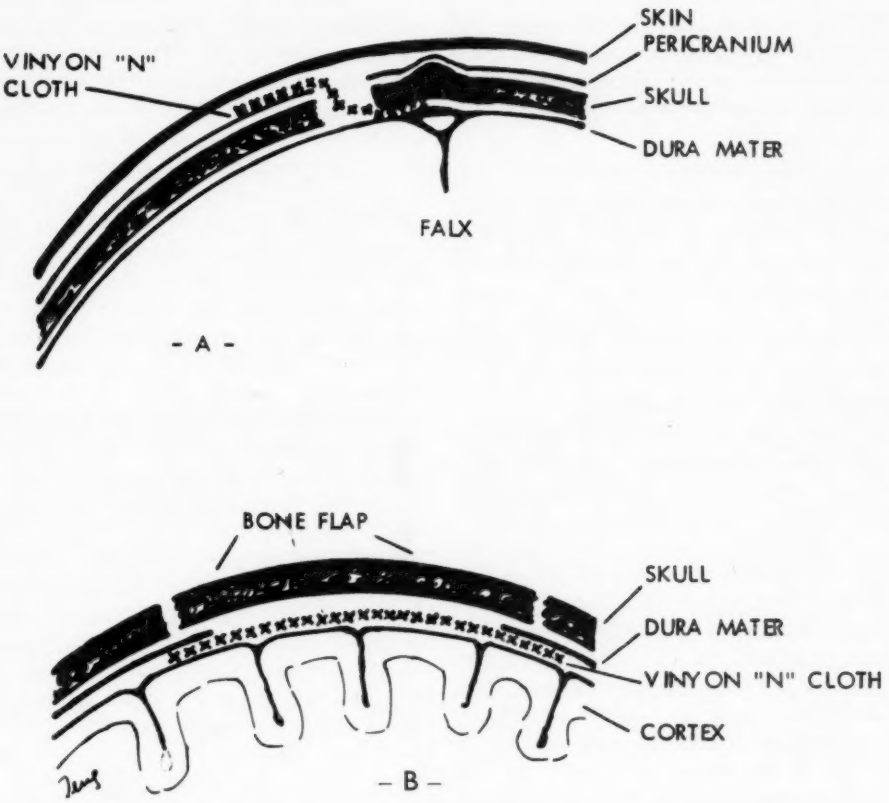

FIG. 1.—Diagram of intracranical use of Vinyon "N" cloth. (A) As bone lining in craniostenosis. Line of cross indicates position of Vinyon "N" cloth lining bone incision. (B) As dural substitute. Note dural cloth tucked under edges of dural defect.

thigh, with subsequent prolonged infection. The right sciatic nerve was partially injured, and pain developed in the right lower leg and foot from this injury. He was operated upon three times at other hospitals, both in the United States and Europe, in an attempt to relieve the pain. After each operation, the pain was partially relieved for a few weeks up to two months, then recurred with increasing severity. For the past one and a half years he has been disabled because of the pain.

On April 29, 1959, the right sciatic nerve in the upper and middle thirds of the thigh was delivered by sharp dissection from an area of extensive cicatrization, which extended through almost the whole thickness of the posterior compartment of the upper thigh, and measured 8 × 4 in. in size. The sciatic nerve was wrapped in a tube made of Vinyon "N" cloth, with the upper and lower ends of the tube placed above and below the field of cicatrization.

Since his last operation 14 months ago, the patient has been free of pain, and there is no evidence of irritation to the sciatic nerve caused by the synthetic cloth.

As Bone Lining in Craniostenosis after Craniectomy.—In six infants with craniostenosis, ranging in age from 1 to 7 months, Vinyon "N" cloth was used as bone lining after craniectomy, to prevent reunion of the bone edges. In all six cases only the sagittal suture was prematurely closed. The surgical treatment consisted of a simple unilateral parasagittal bone incision made 1·5 cm. lateral to the midline. The anterior end of the bone incision (or the artifical groove) extended 1·0 cm. beyond the coronal suture, and its posterior end extended 1·0 cm. beyond the lambdoid suture. A thin strip of Vinyon "N" cloth was used to line the bone edges of the craniectomy. The outer half of the Vinyon "N" cloth was tucked under the outer bone edge between the bone and the periosteum-dura, and the inner half of the cloth was buried under the skin medial to the incision between the galea aponeurotica and the pericranium (Fig. 1A). This procedure is simple, and less traumatic than the multiple bone incisions usual in craniostenosis. The shape and contour of the skull appeared normal one to three months after surgery. The cases were followed for a period of nine and a half, nine and a half, 10, 38, 52, and 52½ months respectively. Radiological study showed no evidence of bone union or bony bridges across the incision. Repeated

clinical examinations revealed no indication of untoward reaction in any of the six cases. Furthermore, Vinyon "N" cloth is soft, silk-like, and it is easy to use in lining the bone edges.

Discussion

The purpose in using a dural substitute is not specifically for the covering of a dural defect but rather for (1) prevention of meningocerebral cicatrization in cerebral lesions caused by either injury or surgery, (2) repair of cerebrospinal fluid fistulas, and (3) preventing adhesions to the spinal cord or cauda equina in instances where the dura cannot be approximated without tension.

The normal dura has no cellular lining, but a fibrous wall with naked fibroblasts. It is analogous to any connective tissue structures when exposed or damaged, being capable of proliferation or regeneration (Leary and Edwards, 1933). Through this so-called ability of regeneration, the dura can bridge over a wide defect. The regenerated dura is formed mainly by the proliferation of fibroblastic cells in the adjacent soft tissues rather than from the edges of the dural defect. Keener (1959) demonstrated that dural regeneration adjacent to bone, *i.e.*, in the upper calvarium, is inadequate, whereas regeneration is adequate when the dural wound is adjacent to soft tissues such as the temporal or suboccipital muscles. The same cells that can repair a dural defect are also capable of forming scar tissue. The use of a dural substitute, therefore, is not meant to replace normal dura but to prevent extension of scars onto cerebral tissue. Vinyon "N" cloth as a dural substitute satisfactorily serves this purpose. It prevents the formation of meningocerebral adhesions and cross-circulations. Its irritative effect is minimal. This has been adequately demonstrated, both in animal experimental studies and in the clinical applications as described above. The amount of the connective tissue formed between the Vinyon "N" cloth and cerebral cortex, after being buried intracranially three to four years, was minimal. In none of the patients treated in this series has any untoward effect been noted in repeated clinical examinations.

Several authors have stated that one of the qualities of Vinyon "N" cloth which makes it unsuitable as dural substitute, is in its fine pores which render it permeable. However, we have found the opposite to be true. In 1953, in animal experiments with Vinyon "N" cloth, it was originally used as an aortic graft, the material being crudely sutured in tube form and anastomosed to the aorta of dogs. For a few minutes, perspiratory drops of blood were seen to penetrate its pores, but shortly afterwards they stopped completely, the pores having been sealed by blood protein. In like manner, when it is used as dural substitute, the exudate of the wound renders the Vinyon "N" material waterproof. Furthermore, the dural substitute does not necessarily have to be waterproof, except when it is used to cover a cerebrospinal fluid fistula in rhinorrhoea, and in the latter condition, Vinyon "N" cloth can be used successfully to seal the fistula.

Its use in craniostenosis, for the prevention of bone reunion after craniectomy, has also shown gratifying results in this series. It is easy to use for lining the bone incision. For as long as 52½ months, there has been no indication of bone reunion or bridge formation across the bone incision.

In severe cicatrization of peripheral nerves, Vinyon "N" cloth has been used satisfactorily as a nerve wrap after neurolysis.

Summary

Vinyon "N" cloth, a synthetic fabric, has satisfactorily been used as a dural substitute, peripheral nerve wrap in cicatrization, and bone lining in craniostenosis after craniectomy in 40 clinical cases. The period of observation ranged from four to 52½ months.

The material is relatively inert and not toxic. It is not absorbed, and has a tensile strength like that of China silk. It can be sterilized by boiling in water. The fine pores in the cloth do not hinder its use in repairing cerebrospinal fluid fistulae, for the serum protein in the wound itself rapidly seals the pores, thus rendering it waterproof.

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THE CASE NOTES OF THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC, QUEEN SQUARE, LONDON, BEFORE 1900*

BY

RICHARD A. HUNTER and L. J. HURWITZ

The case notes of the National Hospital present a unique opportunity of following the development of clinical neurology in the second half of the nineteenth century since for much of this time it was the only hospital specializing in neurological diseases. It is owing to the foresight of the hospital's early physicians and administrators that from 1863—three years after its opening—the in-patient records are preserved complete and they give a vivid picture of clinical neurology as it was practised and developed during those early years.

The earliest case book covering the period 1863-67 consists simply of the patient's history, a note of obvious physical signs, medicines given, and diagnosis. Figures 1(a) and (b) shows the notes of a patient with aphasia and left hemiplegia written in 1865. Dr. Hughlings Jackson's interest in this combination is apparent from his pencilled request to see the patient.

From 1867 the notes became more substantial and consisted of an out-patient sheet bound with the in-patient notes. The in-patients' notes were now made up of a front sheet giving personal details, dates of admission and discharge, duration of illness, result of treatment, diagnosis, and the name of the physician under whose care the patient was; later the names of the house physician and clinical clerk were also recorded. There follow continuation sheets, treatment card, fit charts in epileptic cases, in febrile cases temperature charts which included recordings of pulse, respiration, weight, and analysis of urine; not infrequently sensory and perimetry charts, clinical and post-mortem drawings and photographs were also included. Occasionally, correspondence from referring doctors or other consultants was preserved.

Figure 2 shows a photograph in the case notes of a patient of Dr. Thomas Buzzard in 1875 diagnosed as hysterical ptosis. Note the absence of compensatory contraction of the frontalis muscle on the affected side, which helps to distinguish the condition from this cranial nerve palsy. Incidentally, there is also a photograph of her normal appearance after treatment.

At the end of a year each physician's notes were bound in a volume in alphabetical order to which was prefixed an index of patients' names and diagnoses. In 1880, a separate diagnostic card index was established, and as the number of patients in the hospital increased, the notes of men and women were bound separately. These volumes are now arranged on shelves around the walls of the registrar's room in the Out-patient Department, which is in

FIG. 2.—Photograph of a patient of Dr. Thomas Buzzard illustrating hysterical ptosis by the absence of compensatory contraction of the frontalis muscle, 1875.

*This paper was read at the National Hospital centenary celebrations on June 22, 1960.

1865

May 16. Amelia Bristow – 43 Abbeson Hall Kent par.
Dorset St. Clapham Rd –
married, 3 children living –
Previous health very good –
2 months ago, without any premonitory symptoms, suddenly lost her speech – She never lost consciousness – Her left arm felt weak numb, & she was unable to use her hand for unbuttoning her dress. She could not utter a single word for about ½ an hour. She affirms that she never dragged her left leg, & that the limb never felt numb or in any way impaired.
Her left cheek hung down very peculiarly; she bit the inside of that cheek; drink ran out of the left angle of the mouth – whilst the right angle was drawn upwards & outwards. Since then, there has been no increase of the weakness of the arm – But there has been difficulty of speech ever since, occasionally total loss of speech – not of articulation merely – but of the faculty of possessing in thought the right words.

Present state: Incomplete left facial paralysis – left angle of mouth dragged; left eye closes both eyes well; bites left side of tongue – but there is no appreciable paralysis of the organ – She can protrude it well straight – more it in all directions. She has some difficulty in swallowing; no affection of the 5th pair – sensibility of face & tongue, taste, &c perfect. No headache now; but at time of seizure had dreadful pain in right temple. Memory very bad –; cannot concentrate her thoughts; & her powers very nervous – Hearing good –
Pupils equal, normal; vision good.
Left arm, weak mainly; does not feel cold subjectively or objectively – no tingling; no numbness; no wasting –
Bladder: cannot [illegible]
Bowels: motion, runs away from her involuntarily, although she feels the
Bladder has been affected since a confinement 7 years ago; child still born.
Says that in trying to recall the wrong words makes [illegible]
[illegible]
No albº

369

FIG. 1 (a) and (b).—Case notes of a patient with aphasia and left hemiplegia under the care of Dr. Ramskill, with Dr. Hughlings Jackson's pencilled request to see her, 1865.

Dr – I will see this case & report to Dr Ramskill & Dr Bristowe

June 20. On the 19th began to use wrong sometimes 2 words instead of the right one – knew what was wanted, & knew when had called someone else right but tried to get it, then had a second call another half of body lay not heard what said – was quite sensible of the wrong names & had much use partially affected hand & foot.

Aug 1 Quite rational – Speaks well – Cannot remember names – Much better –

Sept 26 Speech very hesitating, slips her words, says that she often makes mistakes in words; cannot write decipherable letter – cannot return her watch or notes, has lately felt very drowsy.

Oct 10 Apex of tongue deviates to the left; uvula &c. Soft Rousing action
Mist. K.J. c. Ammonia

daily clinical use. The average height of the volumes is 11 inches and the total length of shelf space they occupy up to the year 1946 (when a modern registry was started in which notes are kept unbound) is approximately 860 feet.

On reading the notes one is immediately impressed by the marked similarity between their style and manner of recording the history and that of modern ones. There is the same emphasis on the details of the presenting symptoms.

History Taking

This is well seen in the notes of a 41-year-old man under the care of Dr. Hughlings Jackson from October, 1878, to February, 1879, who had a right hemiplegia and aphasia resulting from a cerebrovascular accident. After an account of his social, medical, and family history, and a note that he was right-handed, his illness as reported by his wife was recorded as follows:

"September 10th, 1878, he came home from work about 7 a.m., having left about 15 minutes before. He said 'he had a dreadful pain in his head, and that he had felt something burst there as he stooped to open the door' . . . All of that day and until September 18th the pain continued 'spreading over the whole of his head, in his eyes and across both shoulders'. During the interval between September 10th and 18th he kept to his bed and at times 'seemed delirious'. At times he was perfectly sensible and would answer correctly and at other times she could not understand what he meant. The periods of incorrect and wondering conversation were longer towards the end of the week . . . The 7th night after the headaches commenced he was talking all night about 'jumping up on the trucks' and 'paving roads'. On September 18th about 7.45 a.m. his wife could not understand him as he stammered and mumbled. He kept looking at his right hand and rubbing it. He got up at 9.30, dressed and walked into the kitchen perfectly well, turned round and walked back to his bedroom. He sat down and seemed 'to be getting very strange'. His wife undressed him and noticed he seemed to be powerless in his right arm and hand. After going to bed the only thing he said was 'yes' which he said distinctly, the next day he did not say it quite so distinctly. His wife noticed that he kept his left hand always on his forehead, as if in pain."

FIG. 3.—Page from case notes of a patient of Dr. Hughlings Jackson showing part of the examination for aphasia, 1878.

Aphasia

Figure 3 shows part of the detail covering many pages with which his aphasia was tested. The notes of 23 November are also of interest in this connexion:

"On the morning of the 21st the Patient attended a concert in the hospital. The first item in the programme was 'God save the Queen'. Next morning after breakfast, while in bed, he was heard mumbling 'God save the Queen' and kept sufficiently to the tune to attract the attention of the attendant who was in the next room. The other patients, epileptic boys, recognized what he was trying to sing. They then joined in with him and appeared to assist him. He kept it up for quite 15 minutes. The words were not perfectly distinct: something like 'Govsavakeen'. Later on the Resident Medical Officer tried to get him to repeat it. He distinctly said 'Save' but could not get out any tune."

The hospital concert just alluded to was one of the regular performances which were sponsored by voluntary workers. Figure 4 shows a representative programme held as part of the "Course of Winter Entertainments for In-patients" in 1874.

Recorded for posterity in the case notes of the same patient is one of Jackson's most pertinent clinical observations relating to respiratory movements in hemiplegia: "The right side of the chest in all parts moves more than the left on quiet breathing; the shoulder rises more on the right, the right lower ribs invert more, the costal angle formed by them is at all times higher. There is, however, more breathing on the left". This manuscript note anticipated by 17 years Jackson's printed account of the difference in hemiplegics between "voluntary" and "involuntary" expansion of the chest (see *Lancet*, 1895, **1**, 476), an example of the value of original rather than printed sources for tracing the development of neurological ideas.

Diagnosis

Although it is surprising how many pre-1900 diagnoses conform to modern concepts, some of course do not. For instance, a 4-year-old boy under the care of Sir David Ferrier in 1890, who was discharged improved after one month, had an eight weeks' history of illness beginning "when he dropped a glass bottle which broke and gave him a fright and this seemed to stupify him so that he remained rooted for 2 to 3 minutes. When removed he began to cry and would touch no food." On examination he was reported to be "drowsy, fretful, and peevish". The nurses reported that "he is stupid and extremely stubborn". No further details are given and there is not sufficient evidence to speculate on which of a number of more serious conditions he may have suffered from. One must therefore rest content with the diagnosis made at the time, which was simply "obstinacy".

Hysteria and epilepsy were not as sharply differentiated as they are today, and fits which are recognizably epileptic were described as hysterical or "hysteroid", especially those accompanied by automatic and other strange behaviour but without the characteristics of grand mal. Many notes of epileptic

National Hospital for the Paralysed and Epileptic,

23 & 24, QUEEN SQUARE, BLOOMSBURY.

Course of Winter Entertainments for In-Patients, 1873—1874.

(BEING THE FIFTH ANNUAL COURSE.)

EXTRA EVENING—THURSDAY, APRIL 16th, 1874.

The Chair will be taken by E. H. CHANDLER, Esq., Hon. Sec.

A Grand Séance Fantastique

OF

Magic, Illusions, Necromancy, &c.,

BY

MONSIEUR EVANION,

The Royal Illusionist, Humourist, &c.

(As performed before their Royal Highnesses the Prince and Princess of Wales, at Sandringham, Oct. 27th, 1866.)

PART I.

INTRODUCTION "Coronation March" (Prophète) ... *Meyerbeer.*
MISS MERRICK.

PART SONG ... "Sir Knight, Sir Knight" ... ... *Pearson.*
PATIENTS, NURSES, AND ATTENDANTS.

PART SONG ... "The Hardy Norseman" ... ... *Pearson.*
PATIENTS, NURSES, AND ATTENDANTS.

Novel Series of Illusive and Amusing Eastern and European Recreations.

1.—CAGLIOSTRO'S CLOCK,
A wonderful piece of mechanism.

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A new and wonderful Feat.

7.—THE ARABESQUE RINGS,
A peculiar and surprising performance.

AN INTERVAL OF TEN MINUTES.

PART II.

INTRODUCTORY OVERTURE—Pianoforte ... MISS MERRICK.

PART SONG ... "My Love has Gone to Battle" ... *Kucken.*

PART SONG ... "Sleep, Gentle Flower" ... *H. Leslie.*
PATIENTS, NURSES, AND ATTENDANTS.

8.—LE MONNAYAGE MYSTERIEUSE,
Interesting Feats of Dexterity and Manipulations.

9.—THE RUSSIAN BELL,
A masterpiece of skill, which cannot fail to astonish even the most knowing.

10.—LES EVENTAILS JAPON,
Japanese Novelties.

11.—LES METAMORPHOSES,
Scene Comique, and Ventriloquism.

12.—ESCAMOTAGE,
The previous explanation of which would diminish the surprise of the spectator.

13.—LE CHAPEAU SANS FIN,
Wonder succeeding wonder.

14.—EVANION'S NEW & WONDERFUL FLAG FEAT,
Multifarious production of thousands of Banners of all Nations.

Doors open for Visitors at Half-past Six; to Commence punctually at Seven o'Clock, and to Conclude at Nine.

FIG. 4.—Programme of a concert for the patients, 1874.

patients contain detailed descriptions of fits witnessed by the nursing staff, whose observations regularly included testing of pupillary responses and limb reflexes. The following is an example of a nurse's note from the year 1888:

"3 p.m. Patient was sitting by the fire in the Day Room. He suddenly covered his face with his hands, made a loud noise in his throat and fell to the right; the limbs were quickly drawn up, right side first then the left. He was very rigid and quite unconscious; the head and eyes were turned to right, face flushed, eyes blinking, pupils dilated; he remained in this condition for about a minute until the limbs relaxed. He then lay struggling and kicking on the floor for about three minutes and continued trying to get up. When he did so he staggered about in a half conscious state muttering different words and sentences. Knee jerks were present during and after fit. Ankle jerks were present during and after fit. Ankle clonus absent during and after fit. Passed water. Did not bite his tongue. Face was flushed all through the attack. Pupils did not become normal till after the fit."

The term "functional" was frequently used in such a context as "functional paralysis" to describe diseases of the nervous system without permanent structural change, as in paralysis with recovery in patients with disseminated sclerosis. This is different from the less exact sense in which it is used today implying a psychogenic rather than an organic origin of symptoms. Such changes in the meaning of terms still in use must be borne in mind in assessing old clinical records.

Medical and Surgical Treatment

There was nothing remarkable in the medical treatment administered at the National Hospital for the period under review. Baths of all kinds came in early as well as physiotherapy. Indeed, physiotherapy and various kinds of electrical treatment were the treatments given in the hospital which received most comment in both the medical and the lay press.

Figure 5 shows a cutting from a newspaper of about 1868 preserved in the hospital scrapbook describing the new wards having the unique feature that to each was attached a day room, the "electrical room", and "a congeries of baths, in every variety". Sulphur baths seem to have been especially favoured in cases of general paralysis of the insane. In 1879 a patient of Dr. Bastian undoubtedly suffering from G.P.I. was discharged after six months' "much improved" following a course of sulphur baths, evidence of the improvement being recorded in serial samples of his handwriting. The writer of his notes—presumably the house physician—concluded: "it may be imagination, but he seemed to improve as

NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC.

Yesterday was a day to be marked in the history of this institution, inasmuch as its scheme of operations was enlarged by the formal opening of additional wards for patients. For this occasion the singular spectacle was exhibited of a hospital *en fête*. There was, in fact, a sort of celebration, for which the whole building was put into a state of ornamentation, and proceedings of a varied character were carried on from one o'clock in the day until after eight in the evening. In the first place, there was an election of five pensioners; for it is a peculiarity of this institution that it has a fund for granting annuities to paralysed or epileptic persons, of the value of £15 and £10. Then came an assemblage of the numerous visitors in the out-patients' spacious waiting-room, and addresses illustrative of the objects and progress of the hospital were delivered by Mr. Alderman Hale, chairman of the board of management, and Mr. E. H. Chandler, the honorary secretary. A special thanksgiving service was then performed by the Rev. J. Buck, rector of St. George the Martyr; the Rev. Gerald Ludlow Hallett, chaplain of the hospital; and another clergyman. A procession was then formed, that marched to the new wards, which were formally opened by the Rev. Mr. Buck. The visitors then dispersed over the building, examining the whole establishment. Here therefore it may well be stated that the hospital was founded in 1859, at the suggestion and chiefly through the agency of Mr. Chandler and his sisters, for the treatment and relief of paralysis, epilepsy, and other diseases of the nervous system, and it found a local habitation in two houses, 24 and 25, Queen-square, Bloomsbury, where the plan was carried on in the cases of both out and in patients, the former being very numerous, under the auspices of a most skilful medical staff. In 1865 it was thought desirable to enlarge and reconstruct the building; and this has been done on a plan of great convenience and perfection of arrangement. It should be said that there is connected with the establishment a ladies' committee, the members of which are indefatigable in their exertions, and it is by their efforts alone that the large sum of £6,000 was raised which has been devoted to making the hospital one of the most comfortable kind. In many of its features it is unique. Thus to each ward is attached a day room, comfortably, and even elegantly fitted up; while the dormitories are models of cleanliness, airiness, and convenience. Amongst the medical appliances is an electrical room, in which machines of every description and power are brought together. Then there was opened yesterday quite a congeries of baths, in every variety, sulphur, douche, vitz, vapour, and, last but not least, a needle bath, which is a Russian invention. As adjuncts to the curative processes, there are gymnasia attached to both the male and female wards, while there is a garden in which air and exercise may be taken by the patients, to facilitate which every variety of wheel chair is to be found on the premises. The front of the building is appropriated to female patients; while the males are accommodated in a separate structure at the back, which is approached by a corridor. Up to the present time no fewer than 8,000 out-patients have been treated, and there are now 1,000 on the books. In the hospital hitherto there have been received 86 patients; the opening of the new wards will enable accommodation to be afforded to 60. Observation on the system pursued in this hospital can lead to no other opinion than that it is in every way a most useful charity, is well managed (it is entirely free from debt), and is in every respect worthy of support from the public.

FIG. 5.—Newspaper cutting describing the new wards about 1868.

long as he took Sulphur Baths, and he rapidly deteriorated during the fortnight while the boilers were being cleaned and Sulphur Baths were necessarily discontinued". "However," he added with that honesty of observation which is apparent in all the notes, "it must be observed that during the same fortnight he was without the Iodide of Potassium".

Counterirritation was much used and ice bags to the spine was a favourite treatment for paraplegia but no particular benefit was noted. Other treatments such as galvanic and faradic currents and hypnosis were, of course, also used. For instance, another patient of Dr. Bastian in 1888 suffering "from functional contracture and anaesthesia of the right arm following an injury at work" was treated with the "strongest galvanic current given for some time without causing the hand to open". Next he was hypnotised by Dr. Beevor who had been a pupil of Charcot in Paris and had produced a testimonial from Charcot in support of his application to the staff of the hospital. However, the only result was to make him "stupid at the time and during the evening". He was hypnotised twice more and each time became "quite unconscious but was not open to suggestions". After the sessions he had "typical hysteroid convulsions". Next he was "put under the ether": his hand relaxed when he lost consciousness but contracted again when he came round. The "actual cautery" was then applied on several occasions, "the only effect" being that he "resented its application". Finally, after three months of various other treatments he was discharged "unchanged".

From time to time outside doctors were also brought in, such as C. L. Tuckey, an eminent London hypnotist, author of *Psycho-therapeutics* (1889) who in 1897 treated a patient of Sir David Ferrier suffering from hysterical paraplegia by suggesting "that he should walk well, with a favourable result".

Some account of the operative treatment practised in the National Hospital during the early days was given by Jefferson in his Victor Horsley centenary lecture (*Brit. med. J.*, 1957, **1**, 903). The first craniotomy was performed in the hospital in 1886; the first successful operation for removal of a spinal cord tumour in 1887; and the first carotid ligation in 1889 on a 39-year-old man who had come to the National Hospital from California, U.S.A., complaining of severe persistent headaches which were tentatively diagnosed as being due to an intracranial aneurysm. Among the many interesting features of his notes are the detailed records kept by Marcus Gunn, ophthalmic surgeon to the hospital. They contain the first observations on the effect of orbital and carotid compression on the retinal blood vessels. On March 11, 1889, Gunn wrote to Sir Victor Horsley: "I saw the 'carotid man' again on Friday . . . There is no doubt that at the operation, compression of the common carotid was followed after a short interval by a slight diminution in the size of the retinal veins but they seemed again to increase to the normal size while the compression was kept up. No change could be noted in the arteries, probably on account of their really shrunken condition so the amount of blood entering the rest of the vessels could be best gauged by the size of the veins. On ligature of the artery a similar slight temporary diminution in size of the retinal veins was observed. On the third day after ligature the veins of the right retina had regained their large size noticed before the operation and in fact were of the same apparent size as noted about a minute or so after the first ligatures. It was now found that light digital pressure on that globe did not evoke the marked arterial pulse observed previously to the operation. A considerably firmer pressure was necessary to do this."

The first ligation failed to produce lasting relief and for reasons which are not clear ligation was also performed on the other side. Not surprisingly a significant degree of dementia resulted. The patient developed "a great scheme by which he is to make his fortune and give employment to thousands of young men" by setting them "to sell bibles at a clear profit of 5 dollars" in all the towns and cities of America—and "what can be done with Bibles, can be done with other things". He abused "Mr. Horsley, Dr. Ferrier, the H.P.s and nurses. Threw a flower-pot through the window today and smashed the glass. When asked why he did it he said 'in order to get fresh air'. Also threw a cup of tea against the wall because he said it was 'swipes' and not proper tea. Refuses to take medicine that is ordered for him, and would not take an aperient though bowels had not acted for a week. Slept with his clothes on several nights; nothing would induce him to undress. Said it made him feel as if he were sleeping out in the forests of America."

Trephining, the oldest operation of which medicine has factual evidence, was of course a not infrequent procedure after Horsley's appointment to the staff in 1886, as well as exploration of the spine and decompression for spinal caries.

Pathology

Post-mortem examinations were performed and recorded in the notes from the mid-1860s but became more detailed over the years and by 1888 included microscopic examination of tumours.

Figure 6 shows the out-patient sheet of a 22-year-

Monday

No. 1251

Under the Care of DR. Gowers

Name Agnes Beadle.

Age 22. Sex F. Occupation Servant.

~~Married~~ or Single

Residence 53. Lockhurst St. Clapton Park.

Recommended by Dr Gowers.

166 Admitted Dec 12th 87 Discharged

CASE.

Diagnosis Cerebellar tumour

Duration

Family History

Previous Health Headaches cutting teeth

History of Disease Pt complains of pains in head — great weakness in legs unable to walk — the weakness came on gradually since last June. pains down the spine at back of head — numbness & tingling sensations in face. Pains in head came on first time accompanied by violent attack of vomiting the pains come on at night in the morning. Memory good. Eyesight better now than some time ago.

to be admitted as soon as possible
WRG

FIG. 6.—Cut-patient sheet with diagnosis "cerebellar tumour" and "to be admitted as soon as possible, W.R.G." in the hand of Sir William Gowers, 1887.

old woman admitted in December, 1887, who died in the hospital in April the following year. Note the readiness with which Sir William R. Gowers diagnosed a cerebellar tumour at his first examination of the patient recorded at the bottom of the sheet in his own hand, signed W.R.G.

Figure 7 shows what appear to be Gowers' own drawings of the post-mortem findings when the tumour was located in the upper midbrain pressing on the left lobe of the cerebellum. On the right are shown a number of tumour cells and for comparison some red blood cells; below them a section of one suprarenal gland which the post-mortem report suggests was atrophic and caseous.

The Neurological Examination

Of great interest to the clinician is the development of case taking and examination to its present-

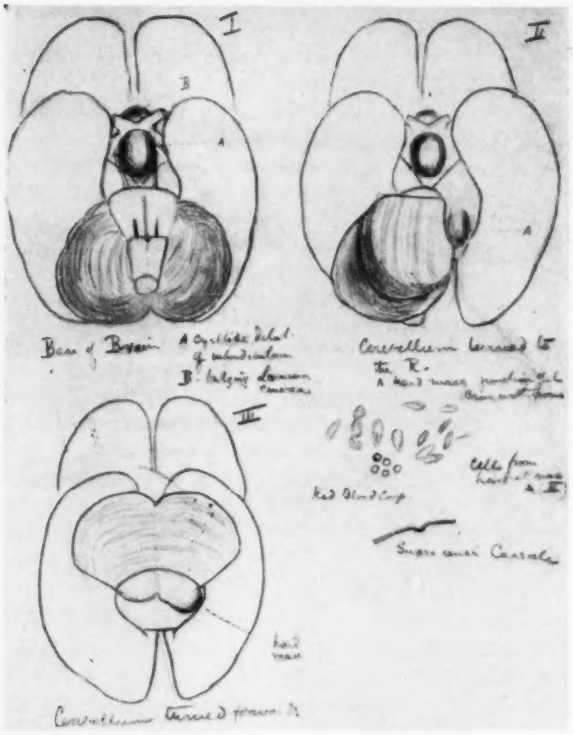

FIG. 7.—Drawings of post-mortem findings in the patient whose out-patient sheet is shown in Fig. 6, probably made by Gowers himself, 1888.

day form as it emerges from a study of these case notes. In the beginning the chief emphasis was placed on the history of the illness and only gross physical abnormalities were recorded. Thereafter, the modern scheme of case taking gradually evolved. By January, 1875, the notes of a patient of Dr. Ramskill were written in the order: family history, social history, previous illnesses, history of present illnesses, on examination, beginning with general physical examination followed by mental state, cranial nerves, spinal nerves, electrical reactions to faradism and galvanism, limb measurements, and finally urine examination. Examination of the extremities was divided into motion and sensation. Hand grip was measured and compared by a dyanometer.

The use of the aesthesiometer for measuring two-point discrimination and examination for tactile localization is also first recorded in 1875, and perimetry charts became general in patients who had visual field defects. In the same year detailed observations for nystagmus, including what is now referred to as the ataxic form, were made and pupillary responses to light first mentioned. Sphygmographic tracings of the brachial and radial pulses were occasionally taken as early as 1878.

Ophthalmoscopy by the indirect method was generally performed by 1870, papilloedema being referred to as optic neuritis. High skill was shown, as for instance when in May, 1878, Dr. Thomas Buzzard recorded seeing what was doubtless a choroidal tubercle "about the distance of a pea to the upper and outer part of the disc there is a rounded yellowish white patch about the size of a small pea". Dr. Jackson also examined the fundus and confirmed Buzzard's finding. The patient subsequently died of tuberculous meningitis confirmed at necropsy.

Pupillary reaction on accommodation was first recorded in 1878 in a patient of Dr. Hughlings Jackson, who was also observed to have absent pupillary reflexes to light. However, the name of Argyll Robertson who had described these phenomena in 1869 does not appear. The patient had lightning or "electricity pains" and absent "patella jerks", and the diagnosis of locomotor ataxy was made. Two years later in 1880 reflex dilatation of the pupils to painful stimuli was first recorded in another of Jackson's patients.

By 1878 cutaneous and deep tendon reflexes were tested in all patients and ankle clonus was recorded. In June, 1880, a patient with a right hemiplegia was noted to have "deficient cutaneous reflexes on the right side" which included testing of abdominal and cremasteric responses. The skin plantar responses were recorded from 1870 but represented reflex withdrawal of the leg on stimulation of the sole. The plantar response in terms of flexion and extension of the big toe and its significance—described by Babinski in 1896—was first recorded in the hospital notes in 1899 when Drs. Collier and Bramwell were house physicians.

Summary

This brief view of the case notes of the National Hospital, Queen Square, shows that by 1880 there had developed a scheme of history taking and examination which approximates to that of today, with the exception only of special investigations. These notes and those of the many other physicians to the hospital formed the basis of the contribution of "Queen Square" to the growing science of neurology: precise, detailed, and unbiased observation of clinical facts recorded in a lively, descriptive style.

We thank the Medical Committee of the National Hospital, Queen Square, for permission to publish.

BOOK REVIEWS

Clinical Neurology. By Sir Russell Brain. (Pp. viii + 399; 67 figures. 38*s*.) London: Oxford University Press. 1960.

The author states that the subject of this book is to serve the needs of those doctors and students who require to know not only the essentials of neurology but to know them thoroughly. More than a third of it is devoted to methods of history-taking and examination, and the discussion of major disorders of function, including unconsciousness, epilepsy, and headache. Part II comprises disorders of anatomical regions ranging from intracranial tumour to disorders of muscle, and is followed by sections dealing with infections, and diffuse and systemic disorders. The final section deals with psychological aspects of neurology, and the introduction to this chapter presents with admirable clarity the need for a balanced approach to the problems of psychological illness, taking into account the unity of brain and mind.

The book is comprehensive to an extent that should well satisfy the needs of those for whom it is written, and although the account of many diseases is brief the essentials are lucidly presented. It is inevitable that in reading a work of this kind the reviewer should find cause for dispute, without which indeed the book would be a dull one. It is in fact the opposite, provocative of thought and question. To take a few points, the diagram of the cutaneous distribution of the trigeminal nerve includes more than the upper half of the auricle within the territory of the third division, whereas the usual finding after sensory root section is anaesthesia only of the anterior strip of the article, and anterior wall of the auditory meatus. Of arteriovenous malformations in the brain it is said that they may be associated with a facial naevus—the Sturge-Weber syndrome—but the cerebral angioma in this syndrome is not of the arteriovenous type.

In the discussion of head injuries the time-honoured distinction is made between concussion and contusion, without reference to recent experimental and pathological observations indicating that irreversible damage to nerve cells and fibres may occur in the absence of bruising or vascular lesions. Meralgia paraesthetica is attributed to construction of the lateral cutaneous nerve as it passes through the fascia lata of the thigh. Many neurologists have abandoned this interpretation in favour of that originally proposed by Stookey, namely, angulation and compression of the nerve at its emergence from the pelvis.

These, however, are minor criticisms of a book which provides in an attractive form a sound introduction to the principles and practice of neurology and will encourage the student to think for himself.

Practical Neurological Diagnosis, 6th ed. By R. Glen Spurling. (Pp. xviii+284; 68 figures, 54*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1960.

This, the sixth edition of a small monograph on neurological diagnosis as applied to the central nervous system, concentrates upon the techniques of history taking and physiological examination as befits the requirements of senior medical students and house officers. It purposely excludes considerations of neuroradiology and electroencephalography, but it gives sufficient details of relevant neuroanatomy and neurophysiology to make the reasons for the clinical examinations understandable. It is well illustrated, and it includes many well-known diagrams such as those of central nervous system pathways, which have been copied with acknowledgments from standard reference books. In most respects it has been brought up to date, as for instance in a chart of the segmental sensory distribution of various spinal nerves attributed to Dr. Percival Bailey. A minor blemish therefore is the incorporation in figure 21 of the electrically excitable cortex on the lateral surface of the brain according to Foerster, showing a representation of motor and sensory functions on either side of the central fissure with the foot and leg areas located on the lateral surface rather than on the mesial surface in the great longitudinal fissure. In this connexion the reproduction of Penfield's homunculi might have proved a wiser choice. However, this book can be recommended for its intended audience.

Neurology Simplified. By David Joseph Lafia. (Pp. xx + 175; 21 figures. 54*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1960.

This book, by a neurosurgeon, is an attempt to make it easy for students and general practitioners to recognize organic neurological disease and to reach a correct diagnosis. It offers little that is not part of normal undergraduate neurological teaching and the method of presentation makes it a difficult book to read.

The Sturge-Weber Syndrome. By G. L. Alexander and R. M. Norman. (Pp. 104; 54 figures. 32*s*. 6*d*.) Bristol: John Wright. 1960.

This monograph is based upon a personal study of seven patients, whose records are described in detail. A chapter is devoted to the neuropathological findings and a short one to the E.E.G. and E.Co.G. findings. The authors have made a careful study of the literature, and they indicate in their valuable list of references those which describe cases of true Sturge-Weber syndrome. From their studies they consider that the essential criteria are a facial naevus and a leptomeningeal angiomatosis. Out of 787 published case records, 257 fulfilled these criteria. Cerebral calcification may not be evident radiologically before the age of 2, and if diagnosis needs confirmation, an examination of the cortex through a

small inspection craniotomy may be necessary. Epilepsy has occurred in nearly every published case, and the authors draw attention to its serious significance. It usually begins in infancy, often as an episode of status, and mental deterioration sets in sooner or later. Operation was carried out in five of the authors' seven patients, the indications being to control epilepsy, to diminish behaviour disorders, and to improve educability. The authors make a good claim for early operation, for they point out that the lesion appears 'to be unique in its epileptogenic property' and these patients often need admission to an institution in later childhood and usually die in status at a relatively early age. This book is a valuable contribution to the subject, and will be read with profit by paediatricians, neurologists, and neurosurgeons. The material is presented so as to emphasize the variety of problems in embryology, neurochemistry, and epilepsy. The production is excellent, although by modern standards the book is not expensive.

Electrical Studies on the Unanesthetized Brain. A Symposium with 49 participants. Edited by Estelle R. Ramey and Desmond S. O'Doherty. (Pp. xiii+423; 224 figures. $6.00.) New York: Paul B. Hoeber. 1960.

Recently developed techniques make it possible to place electrodes accurately in deeply placed brain structures for purposes of recording or stimulation. Whether these methods will improve the surgical treatment of epilepsy is doubtful, but they are certainly adding greatly to knowledge of the functions of the limbic system and other primtive organizations which help to provide the drive to live and do. These pages provide a useful account of present knowledge in this startling field.

The Electrical Activity of the Nervous System, 2nd ed. Edited by Mary A. B. Brazier. (Pp. 273. 35*s*.) London: Pitman Medical Publishing Co. 1960.

The new edition of Dr. Brazier's book incorporates some recent developments in neurophysiology, and some portraits of famous physiologists. The treatment throughout is selective but uncritical with a minimum of discussion. Physiologists derive their knowledge from experiments on a number of animal species, and it is unfortunate that in presenting the facts and figures there is often no mention of the species from which they were derived. The book is, however, clearly written and well illustrated and can be read with advantage by all students beginning the study of neurophysiology.

Rayons X, Radio-Isotopes et E.E.G. dans L'Épilepsie. Edited by H. Fischgold and H. Gastaut. (Pp. 266; 117 figures, 4 plates, and 44 tables. N.F. 65.-.) Paris: Masson & Cie. 1960.

This book is devoted to the way in which radiology can help in the investigation of epileptics. Radiographs of the skull, air-contrast pictures, and cerebral angiograms are all considered in relation to various diseases of known and unknown aetiology with epilepsy as a presenting feature. The use of radio-active isotopes is also discussed. The book is a useful source of reference to this subject.

Epilepsy and Related Disorders, 2 vols. By William G. Lennox, with the collaboration of Margaret A. Lennox. (Pp. xxv + 574 and xx + 1168; 203 figures. 96*s*.) London: J. & A. Churchill. 1960.

'A medical missionary on furlough . . . from Peking, China . . . my missionary zeal was abruptly transformed from the Chinese to the epileptic'. Thus William Lennox writes of himself (p. 735): the year was 1921 and from that time until his death a few months ago he thought, read, and wrote epilepsy. His life was truly dedicated to the betterment of the lot of the epileptic; this book, in part autobiographical, should be his memorial.

Certainly it is very personal, having somewhat the air of a commonplace book, containing quotations at length culled from many sources, brief biographies of authors, living and dead, case histories in plenty, anything, in fact, relevant, or sometimes irrelevant, which has appealed to the senior author. The whole is loosely held together by the homely phrases of this kind, devoted man. Lennox is at his best on the therapeutic and social problems of the epileptic, weakest on the physiological background of epilepsy, in which field the wider experience of the junior author might have been expected to lead to a clearer exposition. The E.E.G. is also discussed solely from the idiosyncratic viewpoint of Erna and Fred Gibbs, partners with Lennox in much of his early work.

Such a storehouse as this is cannot fail to give pleasure and profit to the reader, even though it may exasperate by its digressions, its diffuseness, and its repetitions. It is too large a book to be read as a whole (though divided in two volumes it is, in fact, a single book, which is emphasized by the absence of an index to the first volume) and as a reference work it is unsatisfactory because the looseness of its structure demands compensation by a meticulous index, which it has not got.

Mental Symptoms in Temporal Lobe Epilepsy and Temporal Lobe Gliomas. By Torsten Bingley. (*Acta psychiat.* (*Kbh.*) Suppl. 120, Vol. 33, 1958). Copenhagen: Ejnar Munksgaard.

Over half this monograph from Stockholm is devoted to a review of the earlier literature on the subject and over 200 references are given in the bibliography. With this background, the author has presented his study of mental symptoms in 90 personally examined cases of temporal lobe epilepsy (16 of which turned out to have benign temporal glioma), and in a further series of 253 cases of verified temporal glioma collected from the files of the neurosurgical clinic of Serafimerlaserettet.

The necessity for accurate definition of terms has been recognized and the clinical, electrophysiological, psychological, and statistical findings have been clearly expressed. One of the main conclusions is that mental symptoms, particularly intellectual impairment, of both verbal and non-verbal functions, were more evident in all groups in which the dominant temporal lobe was involved, being most pronounced in cases of tumour.

Unfortunately, no record of detailed examination of the permanent speech disorders in the cases with glioma of the dominant temporal lobe is given, although the problems of paroxysmal (ictal) asphasia are carefully considered.

The section on handedness and 'brainedness' (the term used for the laterality of the dominant hemisphere) is excellent. The degrees of left- and right-handedness and the relationships with brainedness (pertaining to the temporal lobe only) are fully discussed. The author's figures show that the left hemisphere was dominant in 50% of left handers, and that there was no clear evidence that the two hemispheres were equipotential in respect of language.

This monograph is well written in English and gives a useful account of the subject, even though the effect of temporal lobectomy on the mental symptoms and function is left for a later paper.

Exploration du Cerveau Humain par Electrodes Profondes. [*Electroenceph. clin. Neurophysiol.*, Suppl. No. 16.] By Michel Ribstein. (Pp. 130; 46 figures. NF. 30.-.) Paris: Masson & Cie. 1960.

This study deals with six patients with epilepsy in whom Earl Walker implanted electrodes in the brain. The patients, some of whom are described as having Jacksonian epilepsy, are well studied and documented. As the electrodes are introduced without stereotaxic apparatus, the finer localization must remain doubtful. Studies of the electric activity in various parts of the cortex, the white matter, the caudate and amygdaloid nuclei, the thalamus, etc., are reported. Recordings were also obtained during spontaneous and artificially induced fits.

While the number of cases is too small to come to generally valid conclusions, the findings are interesting and the book contains a useful and very complete survey of the literature.

The Historical Development of Physiological Thought. Edited by Chandler McC. Brooks and Paul F. Cranefield. (Pp. xiii + 401; 8 figures. 45*s*.). London: The Hafner Publishing Company. 1959.

The State University of New York held a series of symposia, and the lectures given then with three other articles comprise this book. The intention was to study the development of physiological thought both as a subject of interest in itself and also as a guide to the future in orientating undergraduate and post-graduate programmes. Some chapters, notably that of Eccles on the development of ideas about the synapse, are reviews of recent developments in limited fields, but most are devoted to subjects that are wider and less technical. Many chapters cover developments in the last four or five hundred years, and deal with man as an integrated being, 'live' and with a 'mind' and 'body'. What these words mean is discussed from various aspects, and the reader is left with the impression that although many would like to adopt a mechanistic concept of life, most are compelled to support the vitalistic view. As most chapters have been delivered as lectures the style tends to be conversational, and the book is easy to read.

A Functional Approach to Neuroanatomy. By Earl Lawrence House and Ben Pansky. (Pp. ix + 494; illustrated. 97*s*.) London: McGraw-Hill. 1960.

This volume by two associate professors of anatomy at New York Medical College, Flower and Fifth Avenue Hospitals, New York City, is a detailed and careful account of the anatomy of the central nervous system written on orthodox lines. There is some account of embryology and the physiological importance of the structures described together with some brief clinical notes. The book is copiously illustrated but some of the diagrams are rather complicated. The bibliography is well selected. The book is written primarily for the medical student but it is certainly more detailed than is necessary for students, other than those taking honours degrees, in this country.

Thymectomy for Myasthenia Gravis. By Robert R. Viets and Robert S. Schwab. (Pp. xv + 143; illustrated. 56*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1960.

This monograph discusses the results of thymectomy in 139 patients with myasthenia gravis operated on at the Massachusetts General Hospital and the authors agree with Geoffrey Keynes that the operation is of real benefit in selected cases in whom a thymoma is not present, the best results being obtained in women under the age of 40. There are chapters on the clinical features of the disease, on the radiology of the thymus, on operative technique, and on post-operative cure. This later is one of the most important aspects in management and the advice given is good but more emphasis might have been given to physiotherapy to the chest in the post-operative period. The outstanding chapter in the book is the historical account of myasthenia gravis by Dr. Viets and there is also a short but excellent chapter on the pathology of the thymus by Dr. Castleman.

Papers on Hemiballismus and the Basal Ganglia (1927-1960). By J. Purdon Martin. (Pp. 60. 7*s*. 6*d*.) London: H. K. Lewis. 1960.

Dr. Purdon Martin's keen interest in the functions of the basal ganglia is well known, and this publication provides a useful collection of his thoughts. The subject is so complicated that courage is required to discuss the physiological mechanisms involved, but the author helps considerably by indicating not only what is known but also by listing the many questions which cannot yet be answered.

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks [American Lecture Series No. 342.] By John J. Bonica. (Pp. xix + 354; 45 figures. 70*s*.) Oxford: Blackwell. 1960.

Dr. Bonica's work on the relief of pain by peripheral nerve block is well known, and his publication of this small textbook on the subject will be widely welcomed. The organization of 'pain clinics' has become an important feature of hospital medical services, and there is no doubt that a special study of this subject is most rewarding. His work is based entirely on nerve blocks, but some will think that the technique of reproducing

pain by a very small injection of 6% saline adds something to the techniques available, especially from the diagnostic point of view.

Diseases of the Nervous System in Infancy, Childhood and Adolescence, 4th ed. By Frank R. Ford. (Pp. xvi + 1548; 215 figures. £11. 16*s*.) Oxford: Blackwell. 1960.

All neurologists know Dr. Ford's textbook, and this new edition will be widely welcomed. Some sections, however, are surprisingly out of date. Thus in acute infective polyneuritis where there is paralysis of swallowing there is no mention of the importance of nursing in the prone position. The use of a cuffed tracheotomy tube with positive pressure respiration has transformed the prognosis in the most severe cases and yet this is not mentioned at all. The section on focal epilepsy is incomplete and inaccurate while the operation of hemispherectomy is not mentioned. The diagnostic features of hereditary tremor are not adequately described. It is surprising to read that plaster of Paris splints are still advised in the acute stage of poliomyelitis; the description of the treatment of the bulbar form of the disease is quite inadequate.

At times the presentation is curiously impersonal. Thus in the section on Wilson's disease the reader might reasonably hope to know the author's experience of treatment, yet there is nothing to indicate in this section that he has ever treated a case himself, and certainly there is no suggestion of a personal opinion about treatment.

Few textbooks of this size can hold their own for many editions and yet there is here a wealth of information which we are all glad to refer to from time to time.

Pediatric Neurosurgery. By Ira J. Jackson and Raymond K. Thompson. (Pp. xvi + 564; illustrated. 125*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1959.

This book is good where it deals with lesions particularly common in children; that in effect is the field of paediatric neurosurgery. But in other matters, *e.g.*, tumours and epilepsy, the book becomes only a guide or notebook to neurosurgery and suffers in consequence. There are 22 collaborators and the best contributions are on congenital malformations, hydrocephalus (which includes a first-class review of various techniques and their results), trauma, and subdural effusions and haematomas. The section on tumours is disappointing, there being some remarkable statements, such as: 'Medulloblastomas occur almost exclusively in males and the same is true for craniopharyngiomas'; That papillomas, pinealomas, and craniopharyngiomas act as 'movable valves'; 'To open the dura widely in the face of increased intracranial pressure invites disaster in all hands except those of the most experienced and fortunate surgeons'.

Neurology, 5th ed. By Roy R. Grinker, Paul C. Bucy and Adolph L. Sahs. (Pp. xi + 1386; 445 figures. 196*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. Toronto: The Ryerson Press. 1960.

This well-established textbook is up to date and comprehensive. The descriptions of disease are concise and well illustrated. There are excellent chapters on neurochemistry, the vegetative nervous system, and on the neurological manifestations of certain mental diseases.

Postvaccinial Perivenous Encephalitis. By Ernst de Vries. (Pp. vii + 181; 23 figures. 38*s*.) Amsterdam: Elsevier (London: D. Van Nostrand). 1960.

Following vaccination a patient may suffer from disease of the central nervous system to which, often, no more specific name can be given than 'encephalitis'. At necropsy one of several different disease entities may be found, such as acute anterior poliomyelitis, or haemorrhagic lesions, or encephalopathic lesions, or perivenous regions of demyelination with microglial infiltration and proliferation. This last is called postvaccinial, perivenous, or microglia encephalitis and it is the main subject of the book, which is based upon the morbid anatomical and histological examination of the nervous systems of 62 patients in Holland who died following vaccination or revaccination after 1925. Of these 26 died of microglia encephalitis following primary vaccination and three died of microglia encephalitis following revaccination. The literature is extensively reviewed both in relation to vaccination and to infectious diseases. The author found that microglia encephalitis has very rarely been noted before 1923, that it does not occur in children under 2 years of age and that it does not occur in re-vaccinated people in whom there is an immunity reaction in the skin. He considers that it is probably not caused by a virus or living agent but is due to more complicated interaction of high molecular substances formed by conditions which is some points resemble allergic processes.

This is an interesting, well-documented book which contains a great deal of information.

A Practice of General Anaesthesia for Neurosurgery. By Robert I. W. Ballantine, with the collaboration of Ian Jackson. (Pp. viii + 152; 68 figures. 27*s*. 6*d*.) London: J. & A. Churchill. 1960.

In his foreword to this book, Mr. O'Connell aptly points out that "in the past neurosurgical anaesthesia has appeared unattractive to some and was avoided for what was considered to be more rewarding work." Fortunately with the dramatic development of the art of general anaesthesia in the last 25 years, made possible by improved techniques, drugs, interest and teaching, this attitude of mind seems now to be obsolete. Anaesthesia for neurosurgical operations provides many problems, and for their successful solution happy cooperation between surgeon and anaesthetist is essential. This book provides an excellent account of the problems, the way they may be overcome, and precise details of the available techniques. It is freely illustrated by diagrams and by copies of anaesthetic charts illustrative of various operations. It is obvious that the authors have had a long experience and are themselves used to the team-work praised by Mr. O'Connell. In their introductory chapter, they indicate that early progress in neurosurgical anaesthesia was due to Dr. Mennell. Without detracting from that tribute, some recognition is also due to the efforts of neurosurgeons in this country, in the twenties

and thirties, particularly Cairns, Dott, and Jefferson, who recognized the problems—particularly the need for light, smooth anaesthesia and a perfect airway, maintained for many hours in awkward postures—who helped their anaesthetists to achieve success, and who more than any others, laid down the general principles for nursing successfully the unconscious patient. The authors are to be congratulated on producing a very readable yet succinct account of their subject.

Clinical Neurosurgery, Vol. 6. Proceedings of the American Congress of Neurological Surgeons. (Pp. 300; 120 figures. 64*s*.; $11.00.) London: Baillière Tindall & Cox; Baltimore: Williams & Wilkins. 1959.

In 1954 the Congress of Neurological Surgeons instituted publication of their Proceedings, at which one or more outstanding neurosurgeons are invited to present several papers, in volume I the late Sir Geoffrey Jefferson was the major speaker. Volume 6 is the edited account of the Eighth Annual Meeting of the Congress, and Dr. A. Earl Walker is the major contributor. He presents articles on topics which reflect his main interests. A brief historical sketch of early neurosurgery; surgery of the brain stem; epilepsy. Other contributors provide chapters on regional hypothermia of the brain, anatomy physiology and traumatic lesions of the brain stem; various neurosurgical procedures for posterior fossa lesions and reviews of stereotaxic operations. Outstanding amongst these are Dr. Walker's on epilepsy which provides a brief but succinct account of recent electrophysiological work on experimental epilepsy and its influence on the views of the genesis of epilepsy in the human; and a review of post traumatic epilepsy from its clinical aspects. A review of Dandy's operations for Meniere's disease, an operation which may now be displaced by the application of ultrasonics to inner ear surgery. An account by Dr. Poppen of experience with vascular lesions in the posterior fossa—10 hamartomas, 23 haemangioblastomas, and 21 aneurysms.

These volumes maintain a high standard. The contributors choose subjects in which they have particular interest and experience, and present them with vigour and personal opinions. A discussion of varying length often provides additional clarification of certain problems. The chief contributor at these meetings must find them stimulating, but exhausting, for each paper is of considerable length (up to 30 pp.) and requires considerable preparation.

Klinische Neuroradiologie. Edited by K. Decker, assisted by H. Fischgold, V. H. Marks, D. L. McRae, J. Metzger, H. Schunk, J. M. Travers, and O. Wiedenmann. (Pp. xvi + 507; 550 figures. DM 230.-.) Stuttgart: Georg Thieme. 1960.

The scope of neuroradiology has increased considerably in recent years and it is becoming progressively more difficult to cover the field satisfactorily in one volume. Decker and his associates are to be congratulated on the textbook which they have written. There are eight co-authors, of whom two come from Munich, two from Paris, two from Boston, and one each from New York and Montreal. Multiple authorship tends to have some disadvantages with dangers of recapitulation, but here this fault can scarcely be found. The advantages outweigh any disadvantages, particularly in the bibliography which has a much stronger international flavour than is to be found in most textbooks. In fact none of the authors take a parochial view and Decker's reading particularly has a very catholic flavour.

The book is very well and profusely illustrated, there being nearly 1,500 pictures. The quality of the illustrations is up to the very high standard expected of Thieme; the paper and print are equally good. Unfortunately the price is inevitably high, about £20. The radiographs are reproduced in positive form, the usual German practice, not favoured universally.

A glance at the format shows how inextricably mixed the investigations of angiography and pneumography have become in neuroradiology. This is the inevitable modern trend which in some respects increases the difficulties for both writer and reader. However, it has to be faced and Decker and his team have handled it well.

It would be invidious to single out any one chapter as being better than another. They are all up to date and authoritative.

Psychiatric Dictionary, 3rd ed. By Leland F. Hinsie and Robert J. Campbell. (Pp. ix + 788. 140*s*.) London: Oxford University Press. 1960.

The new edition of this well-established reference work includes almost 2,000 new entries, and covers as before a wide field in psychiatry and allied subjects. Here, for example, you can find the meaning of *Grübelsucht*, egritude, autonyctobatesis, ischnophonia. The entries are concise and clear, and are fully developed where explanation is necessary.

The Neuropsychology of Lashley: Selected Papers of K. S. Lashley. Edited by Frank A. Beach, Donald O. Hebb, Clifford T. Morgan, and Henry W. Nissen. (Pp. xx + 564; illustrated. 74*s*.) London and New York: McGraw-Hill. 1960.

Lashley will be remembered as a great authority on the experimental approach to the study of animal behaviour and learning. As regards the effect of destructive lesions of the brain, he was more impressed with the importance of the total volume of brain destroyed than with injury to special cortical areas, but his observations were often based on experiments with rats. It is regrettable that such a brilliant thinker and research worker should not have been able to study the effects of small brain lesions in man. However, he expresses clear views on many psychological matters, and said of the relation of brain to mind 'there is no logical or empirical reason for denying the possibility that the correlation may eventually show a complete identity of the two organizations'.

Current Psychological Issues: Essays in Honour of Robert S. Woodworth. Edited by Georgene S. Seward and John P. Seward. (Pp. viii + 360. 42*s*.) London: Methuen. 1960.

This is an example of that difficult, uncertain, form of book production the *Festschrift*. Professor

Woodworth's ninetieth birthday might, perhaps have been more aptly celebrated had some of the contributors distinguished more closely between 'honour' and 'praise', for his reputation as a teacher and as an initiator and moderator of research has long been secure on both sides of the Atlantic and is one to which laudatory exercises can add nothing. Many, perhaps the majority of psychologists in this country, owe to him their first systematic introduction to general and experimental psychology. Many more in neighbouring fields of education, medicine, and social science have known and learnt from his *Psychology—A Study of Mental Life* since it first appeared in 1921. As conservator of the central tradition of laboratory work, neither insensitive to fresh or outlying interests nor distracted by them, he is unrivalled.

The quality of some of these essays is rather diminished by their overt personal reference, but there is a quantity of interesting material. R. C. Davis has a readable and informative historical sketch of physiological psychology in the past half century, J. P. Guilford a scholarly account of Woodworth's interests in psychological measurement, and J. J. Gibson a coherent and pointed discussion of some central points in the theory of perception. N. G. Hanawalt's long and comprehensive review of the past 30 years' experimental work on memory is a useful introduction to important literature not always consulted by the clinical research worker. D. B. Klein has worked hard to evoke appreciation of Woodworth's psychopathological interests, such as they were. On the whole this is a book whose chief appeal, however, will be to the experimental psychologist. It seems a pity that such a work could not have been made more of an occasion of wider attraction.

A Psychiatrist's World: The Selected Papers of Karl Menninger; Foreword by Marion E. Kenworthy; Introduction by Bernard H. Hall. (Pp. xxvi + 931. 80*s*. $10.00.) London: The Mayflower Publishing Co.; New York: Viking Press. 1960.

Karl Menninger is, of course, a major figure in American psychiatry and psychoanalysis. We are told that he 'happens to be' a psychiatrist, also a physician, psychoanalyst, teacher, writer, administrator, theorist, and researcher. He is also an able historian, a militant conservationist, a compulsive collector of books, a sometimes serious bridge and chess player, a labouring horticulturist, and an omnivorous reader. Getting further down the barrel, he is a 'son, a brother, a husband, a father, and a grandfather'. On the occasion of his 65th birthday, some of his friends and colleagues had the excellent idea of conveying to others some idea of his depth, colour, and versatility. This selection of his works is the result of their efforts. For some of these the general psychiatric public will be grateful; but less so for others.

It is difficult to discern the basis of selection. Some of the papers are serious contributions to psychoanalytic literature, some to general psychiatric literature, and some are evidently intended for popular consumption. The contributions to psychoanalytic literature follow fairly orthodox lines. He describes, for example, the investigation of a patient with the common cold: he ascertained that the cold was a re-enactment of the patient's wish to castrate her brother and acquire his penis. A revealing article describes why various medical men choose their specialities. The obstetrician is gratifying his infantile wish to become the mother. Urologists think the penis is the most important organ of the body. The unfortunate proctologist, because of the social taboo on anality, is 'perforce a humble man indeed'.

Amongst the contributions to psychiatric literature a paper on 'The Abuse of Rest' can be particularly commended. The author criticizes the concept of 'nervous exhaustion'. This is a diagnosis which satisfies the patient's ego but is rarely justified except in those patients who have been exposed to prodigious stress, cases of battle fatigue and the like. The contributions to such periodicals as *Harper's Magazine*, the *Women's Home Journal*, *American Forests*, and the *Kansas State Peace Officer's Magazine* are perhaps less worthy of being published in a more permanent form and abound in loose statements and irrelevancies. To one's great surprise he describes Freud as modest and retiring. Although the author is primarily an analyst he is sometimes able to open his mind to the wider world. He commends, in 'A Psychiatric Fable', it is true, a resident who does not use words like libido or Oedipus. The author also supports research into leucotomy, for example, for unbearable pain.

Perhaps the main characteristic of this famous man is his energy. The list of his published writings occupies 17 pages. We would agree with him when he says that in America 'gradually the Freudian ideas have gained complete supremacy'. The author is one of the small group of men mainly responsible for this.

The Integrity of the Personality. By Anthony Storr. (Pp. ix + 174. 15*s*.) London: Heinemann. 1960.

In this small volume, designed primarily for the lay reader, the author seeks to explain the nature of analytical psychotherapy and the basic beliefs about personality on which this rests. He stresses the complexity of the relationship between the therapist and the patient and believes that both have some power, however limited, of determining their future. This is a salutary corrective to Freud's determinism but it is naïve to quote Heisenberg's uncertainty principle in support of these views. The author's emphasis, of course, is on environmental factors in the causation of mental illness and he criticizes the work of geneticists, utilizing their modest statements as criticisms but using a very different yardstick to emphasize the importance of the environment. He says that if a child 'is separated from his mother in infancy, reared in fear and cowed and beaten . . . fear and hatred . . . will exist as part of his adult personality'. We would agree, but this history will not have any predictive value. He may become an inadequate psychopath, a gross neurotic, or a multimillionaire. The child of schizophrenic parents is at least likely to be schizophrenic rather than anything else if he develops a mental abnormality.

Perhaps the most revealing part of the book is the support which the author gives to what most non-

analysts have often suspected that 'the least sophisticated of psychotherapists will admit that he became interested in psychotherapy because of his own emotional problems', that an analyst is 'no better equipped to bring up children than a completely unsophisticated person', and that 'some analysts resemble converts to a religion whose lives are enthralled by their faith'.

It is only the last three chapters which are concerned with the psychotherapeutic process and these are perhaps the most useful. The author warns against various dangers to which the psychotherapist is exposed. He may, for example, fall in love with the patient (which is 'incestuous') or indoctrinate her with his own set of beliefs. He admits that it is difficult to prove that psychotherapy is effective but argues that it is equally difficult to prove that it is ineffective and in any case 'we should be driven into psychotherapy even if we disbelieved in its efficacy', a situation which would be most unsatisfactory.

Stress and Psychiatric Disorder. Edited by J. M. Tanner. (Pp. 151. 21*s*.) Oxford: Blackwell. 1960.

This book is a record of the proceedings of the Mental Health Research Fund Conference on Stress and Psychiatric Disorder held at Lincoln College, Oxford, in July, 1958. It contains the 12 papers given at the Conference together with the discussions following them in a condensed form.

As Dr. Denis Hill points out in his contribution, the concept of stress as an important aetiological factor in psychiatric disorder, is largely a development of the post-war years. There has, however, been much loose thinking about the meaning of the term "stress" and Dr. Derek Richter does well to consider some current usages of the word in different fields.

The main chapters in this volume concern the disorganization of behaviour in man, the disorganization of behaviour in animals, physiological responses to stressors, and the prevention and treatment of psychiatric reactions to stress.

If this volume is to be regarded as a guide it seems that stress is much more likely to produce psychosomatic disorders than neuroses or psychoses: perhaps this is because we know more about the physiological responses to stress than the psychological. It is a pity that psychologists contributed so little to this conference. Within the terms of reference of the authors, however, the contributions are of a uniformly high quality and the Mental Health Research Fund and the authors are to be congratulated.

The Etiology of Schizophrenia. Edited by Don D. Jackson. (Pp. 456; illustrated. $7.50.) New York: Basic Books. 1960.

Schizophrenia provides a challenge to many types of research worker, and this book makes a useful collection of the various possible approaches to the problem, including genetics, biochemistry, and physiology. Perhaps the most significant report comes from a study of the family personal relations, which are probably never very normal in the families of schizophrenic children.

Schizophrenia: An Integrated Approach. Edited by Alfred Auerbach. (Pp. viii + 224. $5.50.) New York: Ronald Press. 1959.

This product of a symposium sponsored by the American Psychiatric Association bespeaks the confidence now placed in convergent studies of schizophrenia: "only an integrated multidisciplinary approach will lead us to effective methods of treatment" says the editor in his preface. The chief methods of investigation here presented are neurophysiological, biochemical, psychological, and cultural. Some of the papers restate findings in inquiries that are widely known; others, such as Roy Birdwhistell's on linguistic-kinesic studies of the disorders of communication in schizophrenia, and Gregory Bateson's cognate review of the disorders of homeostasis in the schizophrenic family, go into less familiar territory. Although findings and conclusions are meagre in comparison with the many speculations and suggestions put forward in this book, it indicates the diversity of approaches now thought promising, and the hard road that must be travelled before it can truly be said that they are integrated.

Die Entfremdungserlebnisse. By Joachim-Ernst Meyer. (Pp. viii + 64. DM 12.60.) Stuttgart: Georg Thieme. 1959.

Depersonalization is so striking a departure from normality and so consistent in its manifest pattern that much has been written about it, without adding appreciably to the initial descriptions and speculations about its origin and pathology. Professor Meyer is the latest to essay relating the occurrence of this syndrome to the internal and the environmental situations in which it developed. Stressing the disturbance of relationship between oneself and the external world which is obvious in this disorder he compares and contrasts it with the obsessional syndrome in which, as another German psychiatrist has maintained, the patient is obliged to react against his will to the outer world which he struggles vainly to ward off: whereas the obsessional's world seems narrow, the depersonalized man, isolated from his surroundings, feels they are unreal. Professor Meyer analyses the lives of non-psychotic patients who were depersonalized and concludes that several quite different causes operate in promoting the condition. Acute depersonalization, for example, may be "emotional stupor" after a traumatic fright; hysterical depersonalization can serve to make reality more tolerable; depersonalization during adolescence may be the outcome of the conflicts of puberty. Although Dr. Meyer's account of his cases and of their response to the thematic apperception test is of interest, and his speculations are ingenious, they do not advance our knowledge of the genesis, the prognosis, or the treatment of this puzzling syndrome.

Neurotische Depression. By H. Völkel; Foreword by G. E. Störring. (Pp. viii + 116. DM 14.40.) Stuttgart: Georg Thieme. 1959.

More than half of this monograph is devoted to the description of 12 patients who were neurotically depressed. The succeeding chapters are concerned mainly with the

pathogenesis and diagnosis of the condition. The discussion of pathogenesis is centred on experiences of loss and threat, the effort to maintain a mental equilibrium, and the complex of wishes, ideas, and aims which make up the design of each person's life. Dr. Völkel, following the exposition of Professor Störring (who writes a foreword to the book) puts much store by the notion that each person's life-design is basically formed by "nuclei of crystallization" which, as the personality develops, are fixed, through strong affective investment, into a dynamic structure. The origins of such generalizations are clear enough, but their application to the problems of neurotic depression adds very little, if anything to our understanding of the clinical problem, nor—what is more important at this stage—to proper statement of the problem. Dr. Völkel makes no reference to the extensive French, British, and American literature on this subject, and is evidently unaware that his study traverses ground now tediously familiar.

Psychoanalysis and Psychotherapy. Selected papers of Frieda Fromm-Reichmann. Edited by Dexter M. Bullard. (Pp. xiv + 350. 56*s*. 6*d*.) The University of Chicago Press (London: Cambridge University Press). 1959.

Many of the most adventurous and influential psychoanalysts of the older generation spent the first decade of their professional career in painstaking neurological studies. In this, as in so much else, they patterned themselves on Freud. Freida Fromm-Reichmann, after she qualified in 1914, spent 10 years in the investigation and treatment of head injuries, under the guidance of Kurt Goldstein. Contact with psychotherapists, especially J. H. Schultz, led to an interest and eventually to a training in psychoanalysis. From the customary concern with the treatment of neuroses she passed to a bold application of psychoanalysis to schizophrenic disorders, in spite of the general view put forward by Freud himself and endorsed by Schilder and many others, that psychotic conditions are unsuitable for such therapy. In the United States, where she lived from 1935 until her death in 1957, she worked constantly in this area of psychiatry, and her publications, here assembled, bespeak the clinical grasp and therapeutic experience which she had at her disposal. She spent the whole of this time at Chestnut Lodge, a private institution where the patients were by no means representative of the general run of schizophrenics, but this did not trouble her as she was concerned with the basic problems that beset the path of any physician who gives psychological treatment to schizophrenics.

The papers show much common sense, a gift for exposition, and an awareness of the pitfalls awaiting the inexperienced, the unprepared, and the self-centred or disingenuous psychotherapist. What one seeks for in vain, as in most accounts of psychoanalytic treatment, is a full discussion of failures and an objective analysis of the sorts of change, the proportions of desirable and undesirable changes that occurred, and the extent to which such changes can be foreseen.

Insulin Treatment in Psychiatry. Edited by Max Rinkel and Harold E. Himwich. (Pp. x + 386; illustrated. 35*s*.) London: Peter Owen. 1960.

The popularity of insulin coma as treatment for schizophrenia has waned greatly in recent years, and may be near eclipse. To reassess the value of this method a conference was held in New York in October, 1958; the papers there presented make up this book. Ten of the speakers were from the United States, four from South America, two from Austria, and one from England. Although interesting clinical and biochemical observations were reported, and technical variations described, there was a predominance of uncontrolled studies of the effects of treatment. The speakers mostly held the view that their impressions about therapeutic success and failure could be depended on, and that strictly controlled trials are unnecessary or misleading: as Dr. Rinkel puts it in his concluding summary, differences in diagnosis and differences in the methods of treatment "prevent logical statistical interpretation". Because of this old-fashioned approach, the material presented fails to justify the editors' conclusion that insulin therapy is still essential in psychiatry.

Chemical Concepts of Psychosis. Edited by Max Rinkel and Herman C. B. Denber. (Pp. xxi + 485; illustrated. 63*s*.) London: Peter Owen. 1960.

An international congress offers a temptingly convenient occasion for getting experts in some subdivision of the main theme to summarize their recent work in such a way that a book can be readily made out of their joint contributions. In this instance the Zurich Congress of Psychiatry in 1957 provided the opportunity, and generous support from some 16 pharmaceutical firms and foundations the material aid, for assembling a number of psychiatrists, pharmacologists, biochemists, and physiologists who have been prominent in research into chemical aspects of the pathology and treatment of mental disorder or into the activity of the healthy central nervous system under varying conditions. The 36 papers read at the symposium and assembled in this book have been arranged in five not very homogeneous divisions, dealing respectively with the history of this field; chemical, clinical, and physiological observations; neuroleptics; the problem of schizophrenia; and theoretical reflections.

It is convenient to have some of these studies juxtaposed with others from a seemingly remote discipline, but on the whole the book lacks the coherence and adequate coverage which can be expected in a well-organized survey of current knowledge, planned directly with that end in view. It does not make up for this by the novelty of its contents: practically all the findings reported were already available in the journals. Its faults, in short, are those of its genre, not of its contributors.

Heilpädagogische Psychologie: Vol. I. Grundätsachen einer allgemeinen pädagogischen Psychologie. By Paul Moor. (Pp. 324; 17 tables. DM 32.80.) Berne: Hans Huber. 1960.

In the German speaking countries psychology still has on the whole closer affinity with philosophy than with experimental science. How wide is the gap which separates such psychology from that mostly taught and

studied in American and British universities is demonstrated by Professor Moor's exposition of the fundamentals of genetic and educational psychology. He mistrusts the logical schemata with which science works: scientific truth, he says, means only that the concept it deals with are logically consistent with one another, and is never truth in the metaphysical or the religious sense. Consequently he is teleological and moral in his approach to the development of personality. He looks at conduct from the standpoint of the child's habits, his vital impulses, his decisions, and his inner attitude and understanding. Half of the book is devoted to statements of the psychological systems of Stern, Adler, Köhler, Watson, Spranger, Jaspers, Jung, Klages, Heidegger, and other notables. The other half examines the development of personality, its structure viewed in its totality as "character", and inner "steadiness" for which he coins a new term. Professor Moor's elaborate exposition of his views does not lend itself to summary statement, nor accord with prevailing modes of thought in genetic psychology; it offers, however, an interesting alternative to the theoretical foundation on which much of our remedial education and child guidance rests.

Epidemiological Methods in the Study of Mental Disorders [Public Health Papers No. 2]. By D. D. Reid. (Pp. 79. 5*s*.) London: H.M. Stationery Office; Geneva: World Health Organization. 1960.

Epidemiology of Mental Disorders. Eighth Report of the Expert Committee on Mental Health [Wld Hlth Org. techn. Rep. Ser. 185]. (Pp. 29. 1*s*. 9*d*.) London: H.M. Stationery Office; Geneva: World Health Organization. 1960.

The value of epidemiological methods in studying the aetiology and course of mental disorders is now widely accepted, and the consequent growth of epidemiological investigations has been spectacular. The Report of the W.H.O. Expert Committee takes cognizance of this, and reviews concisely but comprehensively the technical and other problems of such research. Something more detailed was seen to be necessary for the guidance of psychiatrists and others entering upon epidemiological investigations without practical experience. Professor D. D. Reid consequently prepared a vade-mecum setting out the general principles of epidemiological research, and the possibilities and the limitations of its applications to psychiatry. The outcome is a handy, clear, well-organized and readable booklet, which will be of much value to clinicians engaged in such study of mental disorders.

Psychiatry: Descriptive and Dynamic. By Jackson A. Smith. (Pp. 342. 56*s*.) London: Baillière Tindall & Cox. 1960.

The author has tried, in this concise textbook, to describe the psychiatric syndrome and their dynamics with only minimal reference to areas of controversy and non-medical speculation. He has succeeded in this awkard task. His straightforward account, which follows standard lines, begins with a neutral exposition of the various schools of psychopathology, which leaves the reader with an impression that Professor Jackson A. Smith is tolerantly Laodicean in his attitude towards them all. Similarly in the account of reaction types and methods of treatment a quietly ironic sentence or footnote occasionally relieves the steady, economically expressed flow of his description. The sections on alcoholism and on drug therapy are particularly concise and practical.

Jahrbuch für Jugendpsychiatrie und ihre Grenzgebiete, Band II. Edited by W. Villinger. (Pp. 287; 22 figures, 7 tables. DM 26.-.) Berne: Hans Huber. 1960.

This is, in effect, a journal which appears once a year in stiff covers: in an editorial foreword it is explained that lengthy papers on child psychiatry—the subject with which it deals—cannot easily find a medium of publication in German-speaking countries. The editor of this journal is Professor Villinger of Marburg, the doyen of German authorities in this field: three of the articles come from his clinic, whose fine new building, housing 52 children, is described in detail. The majority of the articles tend to be verbose and bereft of explicit factual underpinning: this does not apply however, to the informative study by Harbauer and his colleagues in Cologne, who compared the mental development of 33 children who were permanently crippled by poliomyelitis with the level attained by a control group of 66 healthy children. Several of the clinical papers, *e.g.*, that of Hilde Mosse on the misuse of the diagnosis "juvenile schizophrenia", and Hunnekens and Kiphard's study of the therapeutic possibilities in brain-damaged children, contain suggestive observations and comments.

Measurement of Subjective Responses: Quantitative Effects of Drugs. By Henry K. Beecher. (Pp. xvi + 494; illustrated. 102*s*.) London: Oxford University Press. 1960.

Almost half this book is concerned with the measurement of pain. This is an important and obtrusive subject which inevitably engages the attention of all clinicians at times. The author points out, as many others have, that although the parameters of pain-producing stimuli and certain common—usually autonomic—responses associated with pain can both be measured within limits, pain itself remains subjective and liable to unpredictable variations of threshold and content, both from person to person and in the same person from time to time. Pain therefore cannot be measured, but some oblique approaches to its estimation can be made, and Dr. Beecher discusses and comments on some of these. Although at times obscured by jargon and perhaps occasionally unmindful of the limited value of statistics if applied to unreliable primary facts, this book is a useful one for all clinicians and especially for those concerned in the work of pain clinics. Its chief value lies in admitting the marked limitations of measurement in subjective responses and in indicating ways of allowing for, and in part circumventing, these limitations.

Community Resources in Mental Health. By Reginald Robinson, David F. DeMarche, and Mildred K. Wagle. (Pp. xxiii + 435. $8.50). New York: Basic Books. 1960.

In 1955, the United States Congress authorized a joint commission to carry through a survey of the national

needs and resources for promoting mental health. This monograph is the fifth to be published in the series of reports prepared for the joint commission. The authors, who are non-medical, are experienced in the organization of welfare activities for large communities. They spent two years in collecting data about the relevant social resources throughout the country and making a more detailed field study of 15 counties which had characteristics typical of their respective regions.

The report contains much factual information about the various social services, It confirms, rather than reveals, the lack in many communities of adequate social provision for people with psychiatric troubles: it also confirms the suspicion that there is no satisfactory yardstick for determining what is adequate (as distinct from ideal) social provision for such people. The monograph is much larger, flabbier, and heavier than it would have been if written firmly and concisely.

Course in Electroencephalography

The International Federation of Societies for Electroencephalography and Clinical Neurophysiology announces that an advanced course in electroencephalography will be held in Marseilles from August 28 to September 2 1961. Application forms for those who wish to attend may be obtained from Dr. O. Magnus, St. Ursula Clinic, Wassenaar, Holland.

International Congress of Neuroradiology

The next international congress of neuroradiology (VI Symposium Neuroradiologicum) will be held in Rome from September 18 to 22, 1961, under the Presidency of Dr. Giovanni Ruggiero. All correspondence should be addressed to Dr. Enzo Valentino, General Secretary, VI Symposium Neuroradiologicum—CIT—Ufficio Congressi, Piazza Colonna 193, Rome.

Congress on Mental Retardation

The second international congress on mental retardation will take place in Vienna from August 14 to 19, 1961. Further information may be obtained from the Secretary of the Congress, Universitatskinderklinik, Wien IX, Lazarettgasse 14, Austria.

International Symposium of Stereoencephalotomy

An international symposium on stereotaxic surgery will be held under the direction of Drs. E. A. Spiegel and Henry T. Wycis on October 11, 1961, at Philadelphia. Enquiries should be sent to Dr. Henry T. Wycis, 3401 N. Broad Street, Philadelphia 40, Pa., U.S.A.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Le Foie Alcoolique de L'Hépatite a la Cirrhose Alcoolique. By P. Etienne-Martin and Cl. Klepping. (Pp. 162; 7 figures and 10 tables. NF 20.-.) Paris: Masson & Cie. 1960.

Nerve Endings in Normal and Pathologic Skin. By R. K. Winkelmann. (Pp. viii + 195; 42 figures. 60*s*.) Oxford: Blackwell; Springfield, Illinois: Thomas. 1960.

Child Guidance Centres [Wld Hlth Org. Monogr. Ser. No. 40.] By D. Buckle and S. Lebovici. (Pp. 133. 20*s*.) Geneva: World Health Organization; London: H.M.S.O. 1960.

Cerebral Palsy and Related Disorders: A Developmental Approach to Dysfunction. By Eric Denhoff and Isabel Pick Robinault. (Pp. ix + 421; illustrated. 93*s*.) London: McGraw-Hill. 1960.

Das Schädelhirntrauma: Leitfaden der Diagnostik und Therapie. By M. Klinger; Foreword by R. Nissen. (Pp. viii + 176; 19 figures. DN 19.80.) Stuttgart: Thieme. 1961.

Markhaltige Faserverbindungen am Hirnstamm der Katze. By S. Burgi and V. M. Buchner. (Pp. iv + 127; 49 figures. DM 39.60.) Berlin-Wilmersdorf: Springer-Verlag. 1960.

Anatomie des Menchen: Ein Lehrbuch für Studierende und Ärtze. By H. Braus; Foreword by E. Elze. (Pp. viii + 832; 545 figures. DM 69.-.) Berlin-Wilmersdorf: Springer-Verlag. 1960.

Rorschachiana VII. 4. Internationaler Rorschach-Kongress, Brüssel, 1-4 August, 1958. (Pp. 187; 14 figures, 9 tables. DM 23.80.) Berne: Hans Huber. 1960.

Experimental Psychology. By Burton G. Andreas. (Pp. xi + 595; 19 figures. 56*s*.; $6.95.) London and New York: John Wiley. 1960.

Mental Retardation in Infants and Children. By Abraham Levinson and John A. Bigler. (Pp. 308; 53 figures. 60*s*.; $8.00.) Chicago: The Year Book Publishers (London: Interscience Publishers). 1960.

Die Chirurgie des Nervus Facialis. By Adolf Miehlke, with an Introduction by Prof. Paul Falk. (Pp. xii + 208; 45 colour and 53 text figures. DM 98.-.) Munich and Berlin: Urban and Schwarzenberg. 1960.

Studies on Medical and Population Subjects No. 16: **Area of Residence of Mental Hospital Patients.** General Register Office. (Pp. iv + 177. 15*s*. 6*d*.) London: H.M.S.O. 1960.

Manuel de Psychiatrie. By Henri Ey, P. Bernard, and Ch. Brisset. (Pp. 1014; 31 figures. NF 100.-.) Paris: Masson & Cie. 1960.

Fear and Depression: Their Causes and Self-Treatment. By Allan Worsley. (Pp. 84 + Foreword + Index. 8*s* 6*d*.) London: George Allen & Unwin. 1961.

The Central Nervous System and Behavior. Transactions of the Third Conference, February 21, 22, 23 and 24, 1960. Edited by Mary A. B. Brazier. (Pp. 475; 201 figures. $7.50.) New York: Josiah Macy, Jr. Foundation. 1960.

Principles of General Neurophysiology Relating to Anaesthesia and Surgery. By Barry D. Wyke. (Pp. ix + 136; 26 figures. 21*s*.) London: Butterworths. 1960.

Structure and Function of the Cerebral Cortex. Proceedings of the Second International Meeting of Neurobiologists (Amsterdam, 1959). Edited by D. B. Tower and J. P. Schadé. (Pp. xi + 448; illustrated. 85*s*.) London: D. Van Nostrand. 1960.

J. Neurol. Neurosurg. Psychiat., 1961, **24**, 205.

EPILEPSY DUE TO SMALL FOCAL TEMPORAL LESIONS WITH BILATERAL INDEPENDENT SPIKE-DISCHARGING FOCI

A STUDY OF SEVEN CASES RELIEVED BY OPERATION

BY

MURRAY A. FALCONER and WALTER A. KENNEDY

From the Guy's-Maudsley Neurosurgical Unit and the Department of Clinical Neurophysiology, Institute of Psychiatry, Maudsley Hospital, London

It is widely known that in epilepsy of temporal lobe origin the epileptic discharges may be widespread, affecting both temporal lobes and even more widely both cerebral hemispheres (Gibbs, Gibbs, and Fuster, 1948; Jasper, Pertuisset, and Flanigin, 1951; Ajmone Marsan and Stoll, 1951), but what is not so well recognized is that a unilateral temporal lobe lesion can also on occasion give rise to bilateral temporal lobe discharges. It is the purpose of this paper to report seven cases in which small focal lesions (glial hamartomas, angiomas, or other neoplasms) too small to distort appreciably the ventricular contours on pneumoencephalography were yet associated with bilateral, seemingly independent, temporal lobe discharges, and to describe the changes which occurred in the E.E.G. patterns after operation. The various cases are listed according to the site of the lesions. These cases were culled from 75 consecutive cases of intractable temporal lobe epilepsy operated on before the end of 1957, as described in a previous communication (Falconer, Hill, Meyer, Mitchell, and Pond, 1955).

Case Histories

Case 1: STA.* (Hamartoma with Oligodendrogliomatous Characteristics).—A 19-year-old boy, referred by Dr. D. Hill, had suffered from the age of 5½ years from sudden losses of consciousness often beginning with an epigastric sensation and a taste. Occasionally an organized visual sensation was also present. Such attacks usually lasted 10 to 30 seconds, recurred once or twice a day, and had proved resistant to drugs. Staring, fidgeting, and masticatory movements had been observed during attacks. He never had major convulsive seizures (grand mal). His birth had been an instrumental one, and his intellectual progress had always been retarded. At the age of 12½ years he was placed in an institution because of backwardness and antisocial behaviour. No abnormality was found on neurological examination. Air encephalography disclosed an asymmetry of the two temporal horns, such that the right horn was slightly reduced (Dr. R. D. Hoare), but in many centres the appearances would have been considered within normal limits. The cerebrospinal fluid was normal. His I.Q. measured by the Wechsler full scale was rated at 68 (V.S. 80, P.S. 63). The family history was negative, and both parents were highly intelligent persons.

Several pre-operative E.E.G. studies with routine scalp electrodes and sphenoidal electrodes under Pentothal narcosis showed three independent foci of spiking activity, a major one over the right temporal convexity and two minor ones from the left and right sphenoidal electrodes. In addition there was some reduction of barbiturate-induced fast activity beneath the right temporal lobe. The left sphenoidal focus sometimes spread to the left convexity.

At operation in February, 1956, a 7 cm. right anterior temporal lobectomy was performed, after confirmation by electrocorticography that there were spike discharges in the temporal lobe below the Sylvian fissure but not above this. He made a good post-operative recovery, apart from a series of focal motor seizures involving the left face in the second post-operative week. The lesions in the resected temporal lobe have been described by Cavanagh (1958, Case 4) as a multifocal glial lesion (hamartoma with oligodendrogliomatous characteristics) involving the uncus, amygdala, and the hippocampal and fusiform gyri.

Since operation this patient has been followed for four years. He exhibits a complete left homonymous hemianopia. He has had no fits or auras since leaving hospital, and he has been off drugs for two years. He has become cheerful and social, and he dresses impeccably. He works in a book store, and goes to dances.

The post-operative E.E.G.s were interesting. One month after operation there was some bilateral wave-and-spike activity, while the contralateral sphenoidal electrode still showed independent spiking. One year later the contralateral spiking had disappeared, but ipsilateral sharp waves were present in the posterior temporal

*Our colleagues in publishing their several papers dealing with various aspects of our material on temporal lobe epilepsy have taken as a convention that each case is designated by the first three letters of the patient's name. This convention facilitates references from one paper to another.

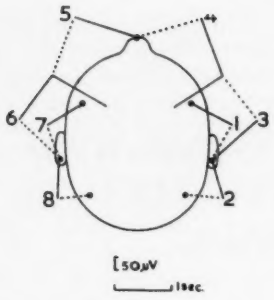

FIG. 1.—Case 2. Pre-operative sphenoidal E.E.G. under Pentothal narcosis shows frequent independent spike discharges at both sphenoidal electrodes. Barbiturate-induced fast activity reduced on the right side.

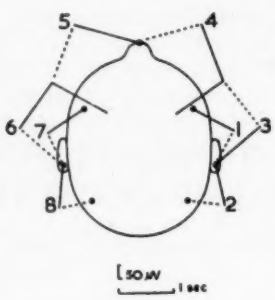

FIG. 2.—Case 2. Post-operative sphenoidal E.E.G. under Pentothal narcosis six years later fails to show spike activity. The prominence of fast activity in channel 1 is due to the craniotomy.

region behind the area of excision. Four years later no spike activity was present.

Case 2: MUN (Hamartoma with Oligodendrogliomatous Characteristics).—A 35-year-old man, referred by Dr. J. P. Dewsbury, while serving as a regular army officer during 1942, first developed attacks of psychomotor epilepsy characterized by epigastric and cephalic sensations with derealization lasting only a few seconds. Masticatory movements as well as confusion had been noted by witnesses, and he averaged one to two attacks a day in spite of medication. He had never had grand mal. A mild psychosexual character disorder developed, and in 1949 he was invalided out of the army. Thereafter he was unemployable, in spite of high intelligence (Wechsler F.S. 138, V.S. 137, P.S. 139) and in spite of several attempts at rehabilitation. The neurological examination, cerebrospinal fluid, radiography of the skull, air encephalography, and right carotid angiograms were all normal.

The pre-operative E.E.G. studies showed frequently firing spike discharges at the right sphenoidal electrode conducted to the convexity. There were also less frequent but independent spike discharges at the left sphenoid electrode (Fig. 1). In addition the barbiturate-induced fast activity was reduced beneath the right temporal lobe (sphenoid-ear channel) and over the right temporal convexity. A Metrazol-induced seizure was inconclusive.

At operation under local analgesia in November, 1954, electrocorticography showed frequent firing in the inferior temporal region with some reduction of normal activity (Dr. G. Pampiglione). Depth electrodes in the region of the roof of the temporal horn were also very active. A 7 cm. right anterior temporal lobectomy was performed. Subsequently he made a good post-operative recovery, with only a minimal left upper-quadrantic homonymous hemianopia. Dr. J. B. Cavanagh (1958, Case 3) reported that the resected temporal lobe contained multifocal hamartomas with oligodendrogliomatous characteristics in the inferior and fusiform temporal gyri and in the amygdala and uncus.

Since operation he has been followed up for six years. Throughout he has been free of fits except for one isolated psychomotor attack in the sixth year after he had been off drugs for several years. He now holds a responsible post on the Stock Exchange and has married.

A post-operative E.E.G. made one month after operation disclosed no spike activity in either cerebral hemisphere, but at 12 months an isolated, ipsilateral sharp wave was observed. Subsequent records up to six years after operation have been satisfactory (Fig. 2).

Case 3: SIN (Oligo-astrocytoma).—A 2½-year-old girl, referred by Dr. K. Cameron, of normal birth and negative family history, had been subject to outbursts of temper for no apparent reason since the age of 14 months. Shortly afterwards minor turns characterized by vacancy, fluttering of the eyelids, nystagmus, and sometimes in-

continence, appeared. These could last from a few seconds to 10 minutes, and could recur as frequently as six to eight times daily in spite of medication. Simultaneously with the appearance of fits, her intellectual development ceased. She had no attacks of grand mal. Neurological examination showed slight weakness of the right lower face, but was otherwise negative. The cerebrospinal fluid was normal. Intelligence testing proved impossible. Radiographs of the skull showed an irregular mass of calcification about 5 × 3 × 2 cm. in the posterior inferior temporal region, while air encephalography showed this to be situated beneath a somewhat dilated but not otherwise disturbed temporal horn. The pre-operative E.E.G. under Seconal-induced sleep showed irregular wave and spike discharges over both cerebral hemispheres, right greater than left, but barbiturate-fast activity was clearly reduced over the left hemisphere.

At operation in February, 1951, a partial temporal lobectomy (7 × 5 × 3 cm.) was carried out including some of the surrounding brain tissue as well as the tumour. The tumour itself was described as an oligo-astrocytoma by Dr. A. L. Woolf, and later reported as such by Cavanagh (1958, Case 7). Her post-operative course has since been one of steady progress. A battery of intelligence tests in the two and a half years subsequent to operation gave I.Q.s ranging from 63 to 77. The psychologist reported two and a half years after operation that she was potentially above an educationally sub-normal level. We have been unable to obtain recent formal intelligence testing, but she is now at a normal school, although working with girls a year younger. She exhibits a complete right homonymous hemianopia.

Follow-up examination after nine years has disclosed a cheerful, alert girl, who has had no fits or auras since operation. Electroencephalographs performed one year, two years, and nine years after operation have failed to show any spike activity.

Case 4: LEW (Capillary Angioma).—A 43-year-old woman, referred by Dr. D. Hill, started experiencing fits 12 years earlier. Her initial attacks were grand mal. Later attacks consisted of dazedness for from one to two minutes, accompanied by clonic movements of the right lower face and right upper limb. She said that they were ushered in by an epigastric sensation and occasionally by a nasty smell. After attacks she sometimes performed such automatisms as dressing and undressing, rearranging of flowers, etc. The frequency of attacks varied, but averaged two or three a week. Over the years she had become paranoid and aggressive. Neurological examination was negative. Skull radiography, cerebrospinal fluid, and air encephalograms were normal. Wechsler full scale I.Q. was 101 (V.S. 104, P.S. 99). The pre-operative E.E.G.s showed an actively firing spike focus at the left sphenoidal electrode conducted to the convexity, and a less frequent but independent focus at the right sphenoidal area. An E.E.G. performed about four years earlier, however, had shown a purely left-sided focus.

In February, 1953, a 6 cm. left anterior temporal lobectomy was performed, after electrocorticography had confirmed the presence of a focus in the left inferior temporal region. The resected temporal lobe was reported by Prof. A. Meyer as showing a small capillary angioma in the uncal region. She subsequently had a smooth convalescence, and has been followed up for seven years. In her seventh year she had two akinetic fits, associated with loss of consciousness, incontinence, tongue-biting. She had been off medication for many years. Her husband reported her personality as much improved.

Her E.E.G.s repeated five days after operation showed no spike activity, and frequent E.E.G.s over the next seven years have failed to show paroxysmal activity.

Case 5: STE (Angioma).—A 40-year-old woman, referred by Sir Charles Symonds, with a normal birth and family history, had suffered from frequent psychomotor attacks since the age of 16 years. Often they were ushered in by epigastric and sometimes also by olfactory sensations. In most attacks she would stare, retch, and fumble, being afterwards amnesic for the attack which might last up to one to two minutes. The earliest attacks were of the grand mal variety. Her present attacks varied in frequency, occurring up to four times daily during her menstrual periods, but with remissions which were seldom longer than two or three days. For the past seven years she had displayed numerous paranoid aggressive outbursts towards her husband and son, as well as towards strangers, and she had had frequent conflicts with the police. Two years before her present admission, at another hospital, radiographs disclosed a shell of patchy calcification deep in the left temporal lobe. (A left carotid angiogram was normal as was a ventriculogram.) Neurological examination was negative, and E.E.G. examinations reported as unsatisfactory because of the patient's poor cooperation. A left craniotomy was performed and an incision 3 cm. long made in the line of the inferior temporal convolution. A mass 6 × 5 × 4 cm. was removed composed of calcified material, fresh black clot, and discoloured brain tissue. It was subsequently reported as an angiomatous malformation. Her surgical recovery from this operation was satisfactory, but no improvement in fits or personality occurred. Her husband left her, and she became a serious social problem. When admitted to our unit her personality was as described. Her fits seemed frequent. No neurological abnormality was found. Radiographs of the skull no longer showed abnormal calcification. Air encephalography, however, showed some dilatation of the left temporal horn, but the left carotid angiograms were still normal.

Pre-operative E.E.G.s, repeated on several occasions, showed bilateral temporal lobe disturbances. Sharp waves and spikes with some slow-wave activity were seen at the left sphenoid electrode spreading to the convexity, but the most active spiking was at the right (or contralateral) sphenoidal area, also spreading to the convexity. This latter activity was independent of the right side. No obvious asymmetry of barbiturate-fast activity was noted, but assessment was difficult owing to the previous craniotomy.

As a lesion had previously been found on the left side the craniotomy was reopened in October, 1953, disclosing a large operative cavity in the left temporal lobe, even

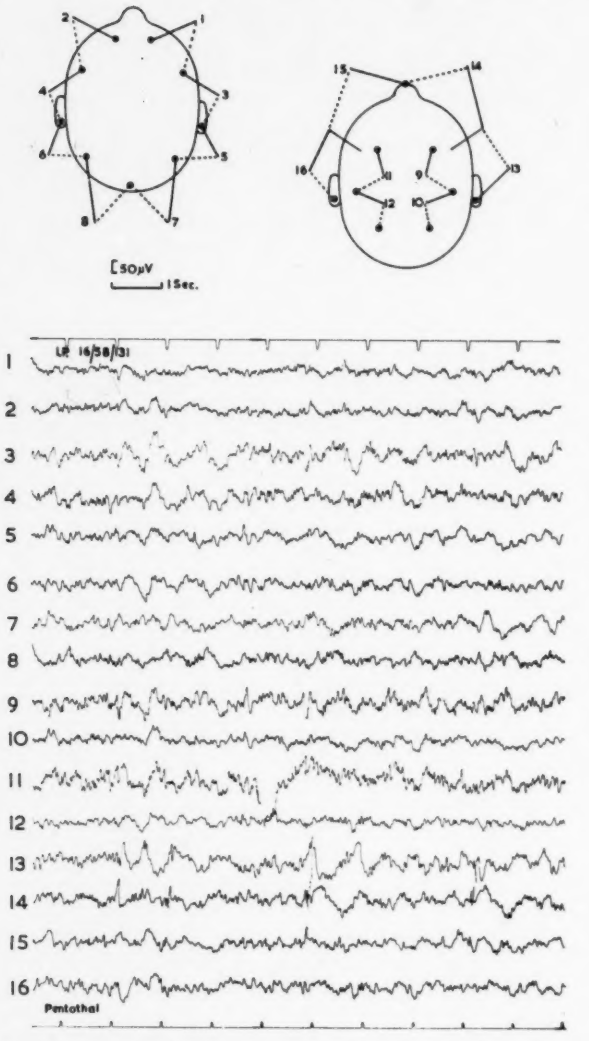

FIG. 3.—Case 6. Pre-operative Pentothal-sphenoidal E.E.G. shows majority of spikes at right sphenoidal electrode (channels 13 and 14). Some are reflected to channel 9.

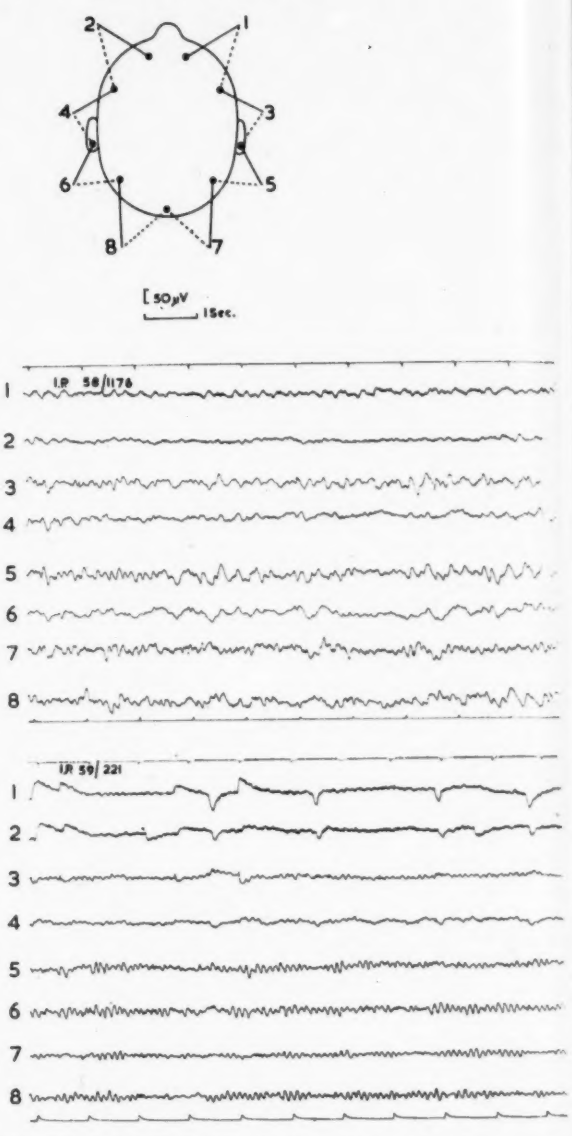

FIG. 4.—Case 6. (*a*) The upper trace three weeks after operation shows no spikes, but some 3 to 4 c.p.s. activity in the contralateral right fronto-temporal region, as well as some post-operative 1 to 2 c.p.s. activity in the left posterior temporal region. (*b*) The lower trace three months later is normal.

although the more active spiking was on the other side. The remains of the anterior 8 cm. of the temporal lobe were removed, including the uncus, anterior 3 cm. of the hippocampus (Ammon's horn), and the amygdala. Professor A. Meyer reported that there were still remnants of angiomatous malformation in the fusiform and hippocampal gyri, and some proliferation of macroglial cells in sectors h3-h5 of the hippocampus. During the post-operative period she exhibited a slight nominal dysphasia, and she required considerable psychiatric after-care. Her personality improved considerably, as did her liability to epileptic attacks. Her home situation has mended itself, and her husband states that she now has not more than four epileptic attacks in any one year, even although she takes no drugs. The follow-up period has now extended over seven years.

A post-operative E.E.G. one month after operation failed to reveal any spikes. Similar findings were obtained six years later.

Case 6: PIN (Hamartoma with Oligodendrogliomatous Changes).—A 23-year-old man, referred by Dr. D. Hill, had suffered from psychomotor epileptic attacks since the age of 13 years, averaging from five to 20 attacks every month in spite of medication. The aura was one of undue familiarity with his environment and also micropsia, and was followed by pallor, staring, humming, and fidgeting with his hands for 30 to 60 seconds. He had also had about 10 grand mal attacks. He spoke with a stammer

but was not dysphasic. Neurological examination was normal. The Wechsler full scale I.Q. was 112 (V.S. 118, P.S. 111). Radiographs of the skull and air encephalograms revealed a small calcified mass in the left temporal lobe situated beneath a normal temporal horn about 7 cm. behind the temporal pole.

Several E.E.G. examinations were performed, and these revealed bilateral temporal independent spike activity in both inferior temporal areas, the right or contralateral side being much the more active (Fig. 3). Each focus of spikes would at times spread to the convexity. Two epileptic attacks were induced, one with intravenous Metrazol and one with intravenous Megamide, and on both occasions the fits appeared to arise in the left temporal lobe.

The problem then arose as to which temporal lobe was at fault. The right temporal lobe was the more active electrically. However, the fact that the induced attacks arose in the left temporal lobe, which was the site of a calcified nodule, led us to undertake a left-sided craniotomy. At operation electrocorticography demonstrated electrical firing to be most pronounced in the anterior temporal region, including the amygdalar region. Electrical stimulation in the region of the calcification produced no clinical effect, but stimulation of the amygdala produced an amnesic attack lasting seven and a half minutes. An 8 cm. anterior temporal lobectomy was performed. Subsequently, he had a smooth post-operative convalescence, and Dr. J. B. Cavanagh reported the lesion as a small gliomatous hamartoma with oligodendrogliomatous characteristics occupying parts of the fusiform and hippocampal gyri. He was left with an upper quadrantic field defect.

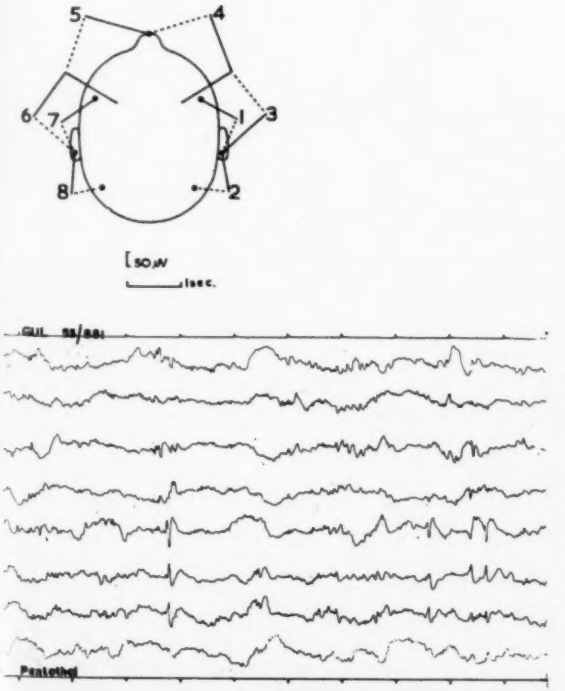

FIG. 5.—Case 7. Pre-operative Pentothal-sphenoidal E.E.G. shows multiple spikes at both temporal areas, left more than right.

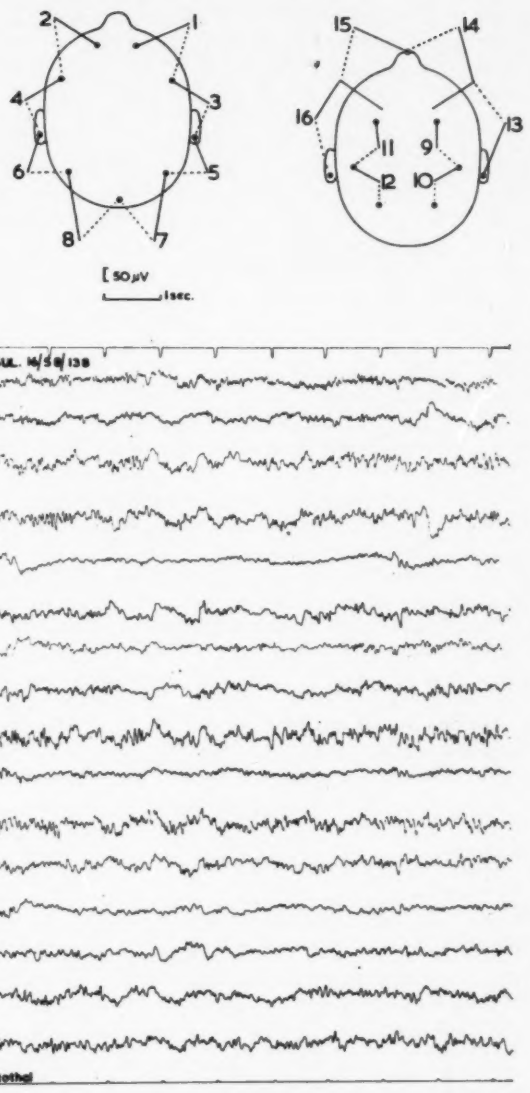

FIG. 6.—Case 7. Post-operative Pentothal-sphenoidal E.E.G. three years later shows no spike activity. Reduction of activity in channels 5, 10, 13, and 14 is due to the temporal lobe resection.

Since then he has been followed up for nearly two years. During that time he has been on medication, and has had an occasional minor seizure. The E.E.G.s taken three weeks after operation showed some unexplained slow activity on the right side, but no spikes. When repeated three months and one year after operation, the E.E.G.s were normal (Fig. 4).

Case 7: GUL (Meningioma of Meckel's Cave).—A 48-year-old woman, referred by Dr. D. Hill, for 10 years had had frequent sudden attacks of pallor and confusion lasting a few minutes, in which she would sometimes repeat stereotyped phrases that bore no relation to her surroundings. There was no remembered aura. Such attacks occurred three to four times a week, and were

resistant to anticonvulsants. There was also a rather vague deterioration of memory. Neurological examination was negative, and air encephalograms suggested some mild compression of the right temporal horn. Intelligence testing showed a Wechsler full-scale I.Q. of 107 (V.S. 107, P.S. 107).

Electroencephalograms showed spike foci at both inferior temporal areas, left more than right, and in addition there was some irregular slow-wave activity at 1 to 2 c.p.s. in the right temporal and right central regions (Fig. 5). This led us to operate on the right side.

At operation in July, 1955, a glioma was suspected, especially as the convolutions towards the temporal pole seemed slightly swollen, and corticography here disclosed slow waves. An 8 cm. anterior temporal lobectomy was therefore performed. After the lobe was excised a small conical meningioma 2·3 cm. diameter by 1·5 cm. high was disclosed coming from Meckel's cave and burrowing into the anterior parts of the hippocampal and fusiform gyri. The cortex of the resected temporal lobe showed Alzheimer type of glial nuclei in the inferior temporal and fusiform gyri (Dr. J. B. Cavanagh).

Subsequently, she was followed up for four years, and during that time a slow but progressive dementia has become apparent. Doubtless she now has Alzheimer's disease. Fits, however, have been infrequent. Since operation E.E.G.s over a period of three years have shown no spike activity at the right sphenoidal area (Fig. 6), and on one occasion only one or two doubtful sharp waves at the left sphenoidal region.

Discussion

The salient features of these seven cases are summarized in Tables I and II. They are all examples of long-standing temporal lobe epilepsy with bilateral temporal lobe spike discharges and have been either cured or substantially relieved by a unilateral temporal lobectomy. Each case had a small focal lesion (gliomas or glial hamartomas, four; angiomas, two; meningiomas, one), and, after temporal lobectomy, spike activity in the post-operative E.E.G. records disappeared on both sides. The lesions involved various parts of the temporal lobe with the possible exception of the hippocampus (Ammon's horn) and the superior and middle temporal gyri. The structures chiefly involved were the fusiform and hippocampal gyri and the amygdala and uncus. It is attractive to believe that these focal lesions were the epileptogenic agents. Favouring this view are the improvement that followed surgical removal in all cases and the fact that in the resected specimens no alternative pathological cause was apparent. The question, therefore, arises as to how these lesions led to bilateral spike discharges, and the mechanisms involved. It is of course well known that unilateral lesions or electrical stimulations of one cerebral hemisphere can give rise to electrical activity with epileptic characteristics in the opposite cerebral hemisphere. The most striking example is afforded by cases of infantile hemiplegia associated with epilepsy, when the presumably normal hemisphere as well as the damaged one are the sites of abnormal electrical rhythms (Krynauw, 1950). The removal of the diseased hemisphere by hemispherectomy is usually followed both by cessation of fits and by a return of normal electrical patterns in the remaining hemisphere. It is not, however, widely realized that small lesions of the type we have described in this paper can also cause bilateral discharges, although this has been previously reported (Kennedy and Hill, 1958; Falconer and Cavanagh, 1959). Yet there is also experimental evidence that this can happen.

We understand that Gastaut (1953) has observed the development of bilateral, seemingly independent, temporal lobe spikes in cats in which alumina cream has been injected into one temporal lobe. Vigouroux, Naquet, and Gastaut (1953) in one particular cat injected the alumina cream in the left amygdala, provoking epileptic seizures within two months, and producing a left temporal lobe spike focus and later a right temporal focus as well. The left temporal area, including the lesion, was then excised and the seizures ceased, but the right temporal focus remained for several weeks. Similar observations were made by Penfield and Jasper (1954) in monkeys in which alumina cream had been injected into the motor cortex on one side. They pointed out that spikes which were transmitted from the primary focus were abolished by section of the corpus callosum, but that secondary independent spikes persisted, suggesting that a true autonomous focus had been established in the homologous area of the opposite hemisphere, presumably due to long persistent bombardment from the primary side. In one particular monkey careful excision of the primary focus containing the alumina cream did not immediately arrest the firing on the opposite side, but a month later the firing was found to have disappeared.

Frost, Baldwin, and Wood (1958) and also Poblete, Ruben, and Walker (1959) have studied in monkeys the propagation of after-discharges between the temporal lobes after electrical stimulation. The first group of authors showed that repetitive electrical stimulation of the second temporal gyrus or of the amygdalar complex was frequently followed by after-discharges in the contralateral amygdala or contralateral second temporal gyrus, but that this propagation could be interrupted by section of the anterior commissure. Poblete and his colleagues came to somewhat similar conclusions. There is thus experimental evidence of close connexions between homologous areas of the two temporal lobes.

Most authors who have operated on patients with temporal lobe epilepsy have stressed that the results are better if before operation the abnormal electrical

TABLE I

CLINICAL AND PATHOLOGICAL DATA OF CASES ARRANGED ACCORDING TO SITUATION OF LESION (PRE-OPERATION DATA IN PRESENT SERIES)

Case	Sex Age	Duration of Epilepsy (years)	Pathology	Situation of Lesion							Type of Epilepsy		I.Q.
				Middle Temporal Gyrus	Inferior Temporal Gyrus	Fusgyrus	Hippgyrus	Amygdala	Uncus	Ammon's Horn	Grand Mal + Psychomotor	Auras	
1 STA	M 15	14	Oligodendroglioma	○	○	■	■	■	■	○	–	Epigastric, organized visual, taste	68
2 MUN	M 35	11	Oligodendroglioma	○	■	■	○	■	■	○	–	Epigastric, cephalic, strangeness	138
3 SIN	F 2½	1	Oligoastrocytoma	Not available	■	■	Not available	Not available	Not available	Not available	–	? Vertiginous	?77
4 LEW	F 43	12	Angioma	○	○	○	○	Not available	■	○	+	Epigastric, smell	101
5 STE	F 40	24	Angioma	○	○	■	■	○	○	■	+	Epigastric, smell	—
6 PIN	M 23	9	Oligodendroglioma	○	○	■	○	○	○	○	+	Micropsia, familiarity	112
7 GUL	F 48	10	Meningioma	○	○	■	■	○	■	○	–	Nil remembered	107

TABLE II

E.E.G, OPERATIVE, AND THERAPEUTIC DATA (OPERATION OR RESULTS IN PRESENT SERIES)

Case	Pre-operative E.E.G. Data					Operation			Post-Operative E.E.G. Data (Spikes)	Therapeutic Result		
	Ipsilateral			Contralateral								
	Convexity (Spikes)	Sphenoidal (Spikes)	Barbiturate Fast	Convexity (Spikes)	Sphenoidal (Spikes)	Extent (cm.)	Side	Follow-up (Years)		Epilepsy	Personality	Work
1 STA	++	+	Reduced	±	+	7	R	4	Nil	5	4	4
2 MUN	+	++	Reduced	+	+	7	R	6	Nil	4·5	4	5
3 SIN	+		Reduced	++		7	L	9	Nil	5	4	4
4 LEW	+	++	?	–	+	6	L	7	Nil	4	3	5
5 STE	±	+	–	±	++	8	L	7	Nil	4	3	5
6 PIN	±	+	–	±	++	8	L	2	Nil	4	4	4
7 GUL	±	+	–	±	++	8	R	5	Nil	4	4	4

In assessing therapy, 5 ranks as excellent, 4 as very good, and 3 as improved.

activity is confined to the resected temporal lobe. The literature on the subject has recently been reviewed by Bloom, Jasper, and Rasmussen (1959-60), and this has also been our own experience (Falconer *et al.*, 1955). Bloom and his colleagues at Montreal, for instance, showed that unilateral temporal lobectomy in a group of 29 cases with bilateral discharges produced successful results, *i.e.*, complete or almost complete abolition of seizures, in only 24% of the cases, whereas in a much larger group of cases with strictly unilateral temporal lobe spiking two out of every three cases were benefited.

Yet the problem remains that certain cases with bilateral spiking can be benefited by unilateral operation, and also that cases with unilateral temporal lobe lesions can be associated with bilateral spiking. Bilateral spiking, therefore, does not necessarily indicate bilateral pathological changes as it is unlikely in the cases we have described that similar lesions were on the other side. This appears to hold true even for mesial temporal lobe sclerosis with Ammon's horn lesions. Thus out of our first 50 cases of temporal lobe epilepsy, 21 presented Ammon's horn sclerosis (Falconer *et al.*, 1955; Kennedy and Hill, 1958) and of these 10 presented bilateral independent temporal lobe discharges, and in eight of them the seizures were abolished (Falconer and Kennedy, unpublished data).

Recently our group have shown that out of 70 cases of temporal lobe epilepsy submitted to unilateral temporal lobectomy for epilepsy on E.E.G. criteria in the presence of normal or only minimally abnormal air encephalograms (which in many centres would have been reported as normal), no less than 15 cases (21%) were due to small unsuspected glial malformations, other tumours, or vascular malformations (Falconer and Cavanagh, 1959). The present seven cases described in this paper (with one exception, Case 6) are taken from that series and illustrate some of the difficulties that arise in the diagnosis and localizations of temporal lobe epilepsy. The disappearance of the contralateral spiking may be delayed (Cases 1, and 7).

It is clear that even when there are bilateral independent spike-discharges in the temporal lobes there may be only a single lesion on one side. In such

cases the patient's seizure may be relieved by a unilateral operation. However, we have as yet no E.E.G. criteria that enable us to forecast with high accuracy where a unilateral lesion is present. There are, however, some pointers. Thus in three of the seven cases described here (Cases 1, 2, and 3) there was definite diminution of barbiturate-induced fast activity on the side of the lesion. In this respect these cases resemble the findings previously described by Kennedy and Hill (1958) in cases with predominantly unilateral Ammon's horn sclerosis. The predominance of spiking by itself is no guide, for in four of our cases (Cases 3, 5, 6, and 7) spikes were more frequent on the unoperated side, and yet the patients were benefited. Three of these cases, however, were selected because radiographs had shown a small calcified lesion on the side which was operated (Cases 3, 5, and 6). The remaining case (Case 7) had irregular slow-wave activity on the operated side. Even radiological evidence of unilateral temporal lobe atrophy is no certain guide, for in a case recorded by Falconer and Cavanagh (1959, Case WAK) there was a very active spike focus on the right side, slight but definite dilatation of the left temporal horn outside the range of the controls. In this case we chose to operate on the E.E.G. rather than the radiological data with a fortunate result in finding a small unsuspected oligodendroglioma. (This patient has been free of fits for six and a half years.) Probably the observance of a spontaneous fit during an E.E.G. examination is of lateralizing value, but such fits may rarely occur. Metrazol-induced activity in our experience can be fallacious, although sometimes helpful (unpublished data). Thus so far the best indication of a unilateral lesion when the radiographs are not conclusive (as in Cases 1 and 2) is a diminution of barbiturate-induced fast activity. In one case the presence of unilateral slow activity was the key to the lateralization (Case 7), while in another E.E.G.s taken several years earlier had shown a unilateral discharging focus (Case 4). With further experience of temporal lobectomy when there are bilateral discharges the criteria for anticipating a unilateral lesion and subsequent relief of seizures may become better crystallized.

Summary

The case histories are recorded of seven patients with intractable temporal lobe epilepsy, generally of long duration, whose electroencephalograms disclosed bilateral, seemingly independent spike discharges in both temporal regions. The air encephalograms showed little or no abnormality, although in three cases a tiny calcified lesion was seen. Each patient was submitted to a unilateral temporal lobectomy for reasons given in the text, and in each a small focal lesion (glioma, hamartoma, capillary angioma, or meningioma) was later disclosed. Subsequently each patient was either cured or very greatly benefited as regards epilepsy, while the spike discharges disappeared, although sometimes after a period of delay. It is presumed, therefore, that the small focal lesions were the epileptogenic agents, and the possible mechanisms by which they caused bilateral spiking activity are discussed. This small group of cases represent an exception to the general rule that unilateral temporal lobectomy fails to benefit more than a minority of paitents with intractable temporal lobe epilepsy and bilateral temporal lobe discharges, and therefore the recognition preoperatively of similar cases is considered. Provisionally, it seems that without radiological evidence of a lesion, diminution of barbiturate-induced fast activity using sphenoidal leads for recording is one of the best indications of a focal lesion, although unilateral slow activity may also be helpful.

We wish to thank the physicians who have referred us their cases, Dr. Denis Hill for his cooperation in the E.E.G. data, Professor A. Meyer and Dr. J. B. Cavanagh for the pathological data, and the Medical Research Council for a grant for the assistance of several research associates. We also wish to thank the Department of Medical Illustration, Guy's Hopsital.

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MENTAL DETERIORATION IN EPILEPTIC CHILDREN*

BY

M. R. CHAUDHRY and D. A. POND

From the Institute of Psychiatry, Maudsley Hospital, London

Epileptic attacks of all sorts are common in children but probably less than a third of them are associated with serious psychological difficulties (Pond and Bidwell, 1960). Of this latter group a much smaller proportion actually deteriorate by the loss of already acquired intellectual and personality functions as the condition progresses. The concept of deterioration in epileptic adults has often been elaborated and the clinical picture is well known (Pond, 1957). Much less is known about children, and the present paper attempts to define the clinical problem as it presents and to investigate the factors apparently related to deterioration. The paper is not concerned with epileptic children who have always been of idiot or imbecile level but with those who have achieved a certain amount of intellectual progress that later is lost. Also excluded are the rare but well recognized neurological degenerations such as the lipidoses.

Material and Methods

The patients for this study were obtained from the Children's Department of the Maudsley Hospital and from the Fountain Hospital for Mental Defectives, Table I shows the basic data in the two groups of cases. Mental deterioration was assessed in the first place by intellectual deterioration as shown by drops in intelligence test scores during the follow-up studies. In addition, there was a social deterioration in almost all cases as shown by a change in the social responsiveness of the children to their surroundings that was noticed by parents, teachers, and employers. A preliminary study clearly showed that all these patients had evidence in one way or another of brain damage. For purposes of a control group, therefore, children from the two hospitals were taken who also had evidence of brain damage, and were matched for age and sex with the deteriorated group. The following two case histories from the Maudsley and Fountain Hospitals respectively illustrate the clinical histories of cases with deterioration.

TABLE I

BASIC DATA OF MAUDSLEY AND FOUNTAIN GROUPS

		Maudsley		Fountain	
		Cases	Controls	Cases	Controls
Total		20	20	8	8
Males		13	10	5	3
Females		7	10	3	5
Age when first seen	M	9 yr. 9 mth.	9 yr. 6 mth.	4 yr. 6 mth.	6 yr.
	r	5-16 yr.	5-18 yr.	2-8 yr.	2-13 yr.
Initial I.Q.	M	85	90	50	45
	r	50-120	62-115	35-75	20-61
Final I.Q.	M	55	85	25	50
	r	40-80	60-112	10-60	22-68
Number of years of follow-up	M	5 yr. 3 mth.	6 yr. 6 mth.	8 yr.	6 yr.
	r	1-12 yr.	1½-10½ yr.	5-12 yr.	2½-8½ yr.

M = Mean; r = range.

Case 1.—P.V., born on June 27, 1943, has been seen in the clinic since 1952. His parents are highly intelligent but very schizoid. There is one younger normal sibling. Paul's birth and early development were normal. Epileptic attacks, at first only major seizures, occurred twice at the age of 2 years, then again twice at 7 years, and then with increasing frequency from the age of 10 years. As well as major seizures and occasionally status, he now suffers from frequent minor attacks, usually brief automatisms or long periods of confusion and inattention. He had the usual childhood diseases without sequelae but no other illnesses.

From 1948 to 1953 he attended ordinary schools but became increasingly disturbed and backward, especially in the last three years. His intelligence test scores were as follows: in 1951, 103 (Binet); in 1953, 90 (Binet); in 1954, 75 (Binet); and in 1957, 67 (Wechsler). Since the last test he has been in a mental deficiency colony and his behaviour precludes adequate intelligence testing. He has become withdrawn and bizarre, with long periods of apathetic staring alternately with aggressive outbursts.

There have never been any abnormal physical signs and the A.E.G. is normal, but E.E.G.s have always been abnormal, showing diffuse, irregular slow spikes and waves and various cortical foci of spikes as illustrated in Fig. 1.

Case 2.—A.P. was born on May 26, 1942, and has been in the Fountain Hospital since 1947. He was a breech delivery after several attempts at version. Although his

*Abstracted from the thesis of one of us (M.R.C.) for M.D. (Punjab).

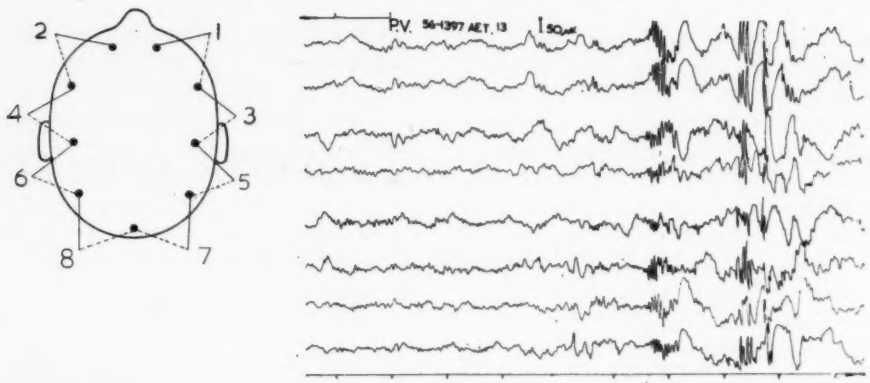

FIG. 1a.—Sleeping record showing normal background activity of sleep interrupted by a symmetrical burst of spikes, fast waves and slow waves.

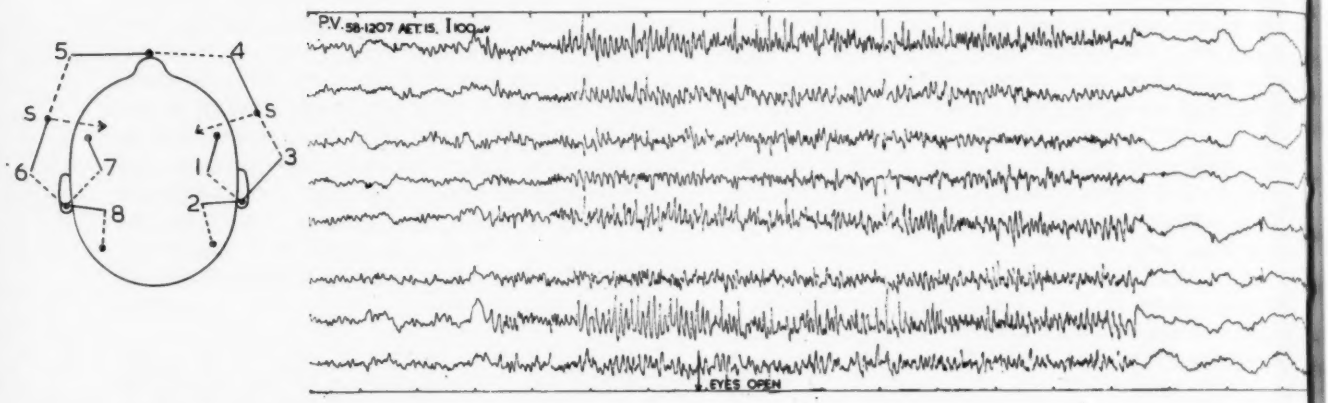

FIG. 1b.—A sphenoidal recording under pentothal showing an unusual generalized brief epileptic attack accompanied by only a minimal change in level of consciousness. Following the seizure spikes are seen at the left base (between channels 5 and 6).

early milestones were said to be normal he was found to be clearly very backward by the age of 4 years when the Binet I.Q. was 45. Up to 1951 he showed slow progress remaining quick, cheerful, but occasionally violent, though able to feed and clean himself. However, he then began to deteriorate, becoming ataxic, perseverative, and incontinent so that he has not been able to attend the hospital school since 1956.

Major epileptic attacks began at 3 months and have continued at about the same frequency of three to four a month in spite of increasing anticonvulsant medication. The abnormal physical signs were doubtful bilateral extensor plantars. An A.E.G. was normal but the E.E.G.s showed at first spikes mixed with generalized irregular slow activity and then later only slow activity.

Results

A variety of psychological tests (Wechsler-Bellevue intelligence scale, Cattell infant intelligence scale, Merrill-Palmer pre-school scale, matrices, and U.S.E.S.) were administered by the psychologists of the two hospitals to these children but the commonest were the revised Stanford-Binet scale and the Wechsler intelligence scale for children. The basic test data are set out in Tables II to V.

Tables VI to IX set out the results of various factors that were investigated and found different or not different between the cases and the controls in the Maudsley and Fountain materials.

The site and extent of brain damage are clearly very difficult to estimate while the patient is still alive. Electroencephalographic (E.E.G.), pneumoencephalographic (A.E.G.), and clinical neurological findings all contribute. In general the E.E.G. shows up only the site of an epileptogenic focus without much being known of its extent. Even pneumoencephalography may show no more than a slight asymmetry of ventricles in cases where subsequent neurosurgery has clearly shown gross pathological changes in the brain. An A.E.G. was done in 11 of the deterioration group and eight of the control group. Diffuse or focal atrophy was found in seven of the deteriorated cases and four of the control

TABLE II

MAUDSLEY CASES

Series No.	Name	Initial Social Status and I.Q.	Later Social Status and I.Q.
1	M.W.	Normal till 6 years 1947 I.Q. = 63	The global intellectual falling off was accompanied by social deterioration (I.C.)
2	P.A.	1954 I.Q. = 100-101	Deteriorated since 1956 (I.C.)
3	R.L.	Normal	1956-57 I.Q. = 60-70 (I.C.) 1957—Temporal lobectomy, no more drop, (still I.C.)
4	O.M.	Normal till 11 years	1956 I.Q. = 50-60 (I.C.) 1958 still needs institutional care
5	E.F.	Normal till 5 years (E.S.N.)	1957 I.Q. = 40-60 (I.C.)
6	M.G.	1955 I.Q. = 105-110	1956 I.Q. = 70-80. Intellectual deterioration between May, 1955, and January, 1956, was noticeable
7	H.J.	Special schooling till 9 years	Ineducable (I.C.) 1958—Temporal lobectomy more S.D.
8	W.M.	1951 I.Q. = 55-70 (E.S.N.)	1952 I.Q. = 45-65. S.D. (I.C.)
9	A.M.	1953 I.Q. = 107	1956 I.Q. = 40-60. Defective (I.C.)
10	M.M.	1946 I.Q. = 79	1952 I.Q. = 46 1954 (I.C.) 1958 further deterioration, (still I.C.)
11	P.B.	1952 I.Q. = 112	1955 I.Q. = 99 1956 (I.C.)
12	G.C.	Normal till 6 years	1950-52 I.Q. = 40-50, Ineducable and psychotic
13	C.R.	1947-49 I.Q. = 105-110	1952 I.Q. = 82, Hopeless work record 1958 still unemployable
14	E.M.	Normal, rather an intelligent girl	1954 I.Q. = 65 1958 I.Q. = 40, Ineducable
15	P.V.	1951 I.Q. = 103	1953 I.Q. = 81, 1954 I.Q. = 75, 1957 I.Q. = 67
16	S.W.	1950 I.Q. = 90	1951 I.Q. = 71, 1953 I.Q. = 52, 1955 (I.C.)
17	L.W.	1947 I.Q. = 82	1949 I.Q. = 67, 1950 I.Q. = 62
18	M.W.	1949 I.Q. = 80-100	1950 I.Q. = 65-70, 1958 Unemployable
19	G.W.	1955 I.Q. = 120	1958 Ineducable, problem for special school
20	L.W.	1948 I.Q. = 105	1952-53, S.D.—considerable decline in social interest

E.S.N. = educationally subnormal.
S.D. = social deterioration
I.D. = intellectual deterioration
I.C. = institutional care (epileptic colony, mental defective colony and special schools)

TABLE III

MAUDSLEY CONTROLS

Series No.	Name	Initial Social Status and I.Q.	Later Social Status and I.Q.
1	B.B.	Normal I.Q. = 75-95	Same range of I.Q. 75-95
2	D.B.	I.Q. = 65-75	I.Q. = 60
3	L.C.	1950 Social Q. = 92	1952 I.Q. = 76, 1953 I.Q. = 73, 1958 Good school report
4	C.C.	I.Q. = 80-90	I.Q. = 80
5	J.D.	1951 I.Q. = 98	No change
6	N.G.	1952 I.Q. = 100 (dull for her family)	No change
7	H.A.	Intelligent girl	Remains intelligent
8	S.M.	I.Q. = 126	No deterioration
9	D.H.	1950 I.Q. = 95	1953 I.Q. = 85
10	D.H.	1952 I.Q. = 62	1958 I.Q. = 64, better at school
11	D.K.	I.Q. = 100-110	Remains normal
12	J.A.	I.Q. = 104	No deterioration
13	S.P.	I.Q. = 77	No change
14	B.P.	1948 I.Q. = 99	1949 I.Q. = 105, 1951 I.Q. = 95. No further change
15	D.R.	1951 I.Q. = 94	Normal
16	A.B.	1955 I.Q. = 70-80	Normal
17	E.S.	1947 I.Q. = 103	1952 I.Q. = 90-110
18	R.S.	1948 I.Q. = 107	1957 I.Q. = 100-110
19	K.O.	1950 I.Q. = 115	1955 I.Q. = 105-110
20	C.W.	Bright child	Remains bright

group. The differences are slight and not significant. In the E.E.G. bilateral foci were seen in half the cases of both groups. Almost all the unilateral changes were in the temporal areas and these again were distributed equally in the two groups and equally between right and left sides in the two groups. Neurological signs were only slightly more common in the deteriorated group than in the controls. In one-third of the patients the histories did not give sufficient evidence to be sure when the brain was damaged. In the other cases the presumed time of damage was at or after birth or later in the same proportions in both cases and controls.

The age of onset of seizures was likewise not different in the two groups which is at first sight surprising since several authors, *e.g.*, Collins and Lennox (1947), have found that the earlier the age of onset of fits the greater the chance of mental backwardness. However, these series include a large number who were defective from the very beginning of their illness as well as those who deteriorated.

TABLE IV

FOUNTAIN CASES

Series No.	Name	Initial I.Q. Level	Later I.Q. Level
1	D.C.	1947-50 I.Q. = 65-75 ESN	1953-54 I.Q. = 50-60 High-grade imbecile
2	A.P.	1947-50 I.Q. = 40-50 High-grade imbecile	1951-54 I.Q. = 20-25 Low-grade imbecile
3	P.B.	1949-51 I.Q. = 35 High-grade imbecile	1956 I.Q. = 20 Low-grade imbecile
4	M.G.	1953 I.Q. = 40 High-grade imbecile	1956 I.Q. = 30 Idiot level
5	E.B.	1953 I.Q. = 40 High-grade imbecile	1956 I.Q. = 14 Idiot level
6	L.K.	1951 I.Q. = 52 High-grade imbecile	1952 I.Q. = 9 Idiot level
7	R.S.	1951-52 I.Q. = 65-75 ESN	1955 I.Q. = 49 1957 I.Q. = 34 1958 Low-grade imbecile
8	M.E.	1951 Normal	1957 Institutional care

TABLE V

FOUNTAIN CONTROLS

Series No.	Name	Initial I.Q. Level	Later I.Q. Level	
1	C.G.	1954 I.Q. = 20	1956 I.Q. = 24	1957 I.Q. = 32
2	D.B.	1955 I.Q. = 41	1956 I.Q. = 47	1957 I.Q. = 49
3	L.P.	1955 I.Q. = 45	1958 I.Q. = 47	
4	S.B.	1954 I.Q. = 25	1955 I.Q. = 29	1957 I.Q. = 22
5	G.A.	1956 I.Q. = 50	1957 I.Q. = 56	
6	R.H.	1949 I.Q. = 61	1951 I.Q. = 65	
7	A.A.	1951 I.Q. = 45	1952 I.Q. = 60	
8	A.W.	1951 I.Q. = 58	1954 I.Q. = 67	1958 I.Q. = 68

The importance of anticonvulsants in producing mental changes in epileptics has been stressed by a number of authors in the past, for example, Stauder (1938) but denied by others, *e.g.*, Loveland, Smith, and Forster (1957). Patients in both cases and the control series had all been on various drugs for various periods and a rating scale had, therefore, to be devised for purposes of comparison. Daily doses of 60 mg. phenobarbitone, or 100 mg. phenytoin, or 0·5 g. of primidone were regarded as approximately equivalent and rated at one point each, larger doses being rated proportionally. Up to three points was classified as a moderate dosage, three to five as high, and above five as very high. Table VI shows that there is no significant difference in the level of dosage of drugs in the controls and the cases, nor is there any difference in the number of years of medication.

A wide variety of emotional and behaviour disorders were seen in both groups but the most important concerned temper tantrums and other aggressive manifestations. These were equally common in both cases and controls.

Finally Table VI shows that there are no significant differences in the family histories of epilepsy in the cases and controls.

Table VII shows similar factors investigated and found not different in the cases of the Fountain

TABLE VI

FACTORS INVESTIGATED AND FOUND NOT DIFFERENT BETWEEN MAUDSLEY CASES AND CONTROLS

	Cases	Control
1 *Site and extent of brain damage*		
Unilateral	9	10
Bilateral	11	10
2 *Presumptive age when brain was damaged*		
Conditions during birth	5	6
Conditions after birth	7	6
Unknown	8	8
3 *Age at onset of seizures*		
Before 6 months	2	1
6 months to 4 years	8	9
After 4 years	10	10
4 *Amount and duration of drugs*		
Amount: Slight or moderate	6	8
Amount: High	13	8
Amount: Very high ($\lambda^2 = 3{\cdot}278$, not significant)	1	4
Duration: 2 to 5 years	4	6
Duration: 5 to 15 years	16	14
5 *Emotional and behavioural problems*		
Disturbance of function	13	13
Conduct disorders	2	—
Nervous traits	1	1
Normal	4	6
6 *Incidence of epilepsy and related diseases (e.g., migraine, mental illness, mental deficiency) in families*		
Epilepsy	6	6
Others	3	3
Negative	11	11

TABLE VII

FACTORS INVESTIGATED AND FOUND NOT DIFFERENT BETWEEN FOUNTAIN HOSPITAL CASES AND CONTROLS

	Cases	Control
Age at onset of seizures		
Before 6 months	3	1
6 months to 2 years	3	6
2 years to 4 years	2	1
Amount and duration of drugs		
Amount: Slight	5	5
Amount: Moderate	3	3
Duration: 2 to 5 years	1	1
Duration: 5 to 15 years	7	7
Incidence of epilepsy and related diseases (e.g., migraine, mental illness, mental deficiency) in families		
Epilepsy	2	1
Others	2	2
Negative	4	5

Hospital material. As would be expected, the cases in this hospital all had an earlier onset of epilepsy than in the majority of the Maudsley cases. Both groups of cases had been on lower anticonvulsant dosage than in the majority of the Maudsley patients and again there was no evidence of any difference between the cases and the controls. In the same way, the family history of epilepsy was not different in the two groups.

Table VIII shows factors investigated in the Maudsley material which show significant differences between the cases and the control groups. The frequency of seizures refers to the time before the patient had been on any regular anticonvulsant treatment. As regards major seizures, infrequency was regarded as not more than one seizure a month;

TABLE VIII

FACTORS FOUND DIFFERENT BETWEEN MAUDSLEY CASES AND CONTROLS

	Cases	Controls	χ^2
Number and type of seizures			
Status or very frequent (M_1 and M_2)	7	2	6·76
Frequent M_1	1	1	
M_1 and M_2	6	3	$P < 0·05$
M_2	3	4	
Infrequent M_1	2	4	
M_1 and M_2	1	6	
Results of medication on seizures			
Controlled (all types)	3	12	
Controlled partially	—	3	
Reduced	15	5	15·0
Unaffected	2	—	$P < 0·001$
Type of E.E.G. abnormality			
Focal	4	15	
Focal and general	13	5	12·92
General	3	—	$P < 0·01$
Previous mental status			
Feeble minded	7	1	
Dull average	3	5	5·664
Average or above	10	14	$0·1 < P < 0·05$
Environmental and social factors			
Disturbed environment	14	8	3·636
Normal	6	12	$0·1 < P < 0·05$

M_1 = major seizures. M_2 = minor seizures.

frequent attacks from two to 10 a month; and very frequent more than 11 a month. In the case of minor seizures, infrequent attacks were less than two seizures a week; more frequent attacks from two seizures a week to 10 a day, and very frequent attacks, more than 11 seizures a day. The difference between the cases and the control groups is significant at the 5% level; the effect of medication on the seizures shows an even more definite difference. In the case of the control groups, all types of attack became very infrequent, but in the majority of the cases the attack frequency was merely reduced.

The E.E.G.s of both the Maudsley and the Fountain cases were done at the Maudsley hospital and reported on by one of us (D.A.P.). They were divided up into the three groups as far as possible without knowledge of the clinical findings. The E.E.G.s were classified as focal only if they showed against a normal background focal disorders, whether these were spikes, sharp waves, slow waves, or combinations thereof. The focal and generalized abnormalities showed not only the focal changes already mentioned, but also generalized irregular disorders such as slow spike-and-wave complexes or an excess of very slow activity of whatever form. Table VIII clearly shows that the patients much more often had a combination of focal and general changes in contrast to the controls, who had mostly focal abnormalities only.

The previous mental status refers to the state that the patient showed before deterioration occurred. It shows that there is a tendency for the already dull child to deteriorate more than those who are average or above. As a group, of course, both the cases and the controls show a range of intelligence well below average since both groups have cases of epilepsy with brain damage.

Lastly, there seems to be some evidence that the social and family environments of the deteriorated child are more disturbed than those of the control cases.

Table IX shows the data on the Fountain Hospital material as regards effects of number and types of seizure, the results of medication, and the type of E.E.G. abnormality. The numbers in these cases are small and no significant statistical analysis can be made. However, the figures show the same general tendencies that were found in the Maudsley material.

TABLE IX

FACTORS SUGGESTIVE OF DIFFERENCES BETWEEN FOUNTAIN HOSPITAL CASES AND CONTROLS

	Cases	Control
Number and type of seizures		
Status and very frequent M_1	5	2
M_1 and M_2	2	—
Frequent M_1 and M_2	1	3
M_2	—	1
Infrequent M_1 and M_2	—	2
Results of medication of seizures		
Controlled	1	3
Reduced	6	5
Unaffected	1	—
Type of E.E.G. abnormality		
Focal	—	3
Focal and general	3	1
General	5	4

M_1 = major seizures. M_2 = minor seizures.

Not brought out in these tables are the various behavioural changes that accompany the deterioration. Confusional periods lasting up to hours are sometimes seen, with or even without preceding major or minor attacks, so that these episodes do not seem to be typically post-ictal. There is also a progressive withdrawal of interest so that the child appears dull, unresponsive, and even at times frankly autistic, with mannerisms typical of the psychotic child. Violent tantrums and rages may alternate with these periods of apathy. Speech often becomes slow and monotonous in delivery with a progressive loss of vocabulary and responsiveness.

Discussion

Before commenting on the significance of this material, some relevant neuropathological findings should be mentioned. Three of the cases and one patient in the control group have had a temporal lobectomy by Mr. M. A. Falconer, in the Guy's-Maudsley Neurosurgical Unit. The neurological data kindly supplied by Dr. J. P. Cavanagh, of the Department of Neuropathology at the Maudsley,

showed diffuse microscopic lesions in all four cases. The changes are similar to those found in other temporal lobectomy cases at various ages and cannot be regarded as in any way specific to deterioration. How far out from the temporal lobe area the diffuse damage spreads cannot, of course, be told from biopsy specimens without full post-mortem studies.

The close correlation with the frequency of seizures and particularly with the efficacy of their control by anticonvulsants makes it tempting to consider that the fits themselves may cause deterioration as has been put forward by a number of authors, particularly Scholz (1951). However, in at least two cases there is clear evidence that the process of deterioration may be reversed, in the one case, following a temporal lobectomy. As this reversibility is an important point, the two cases are briefly described here.

C.F., born on May 14, 1944, was the daughter of a professional man. Pregnancy and birth were normal although she showed considerable feeding difficulties for the first three months of life that were shared with the other children. The milestones of sitting up, walking, and talking were quite normal, but at 2½ years of age she was regarded as abnormally restless. Shortly before her third birthday, a month after the arrival of the new baby, of whom she was obviously jealous, major seizures began and rapidly became daily. The fits often started in the right arm and leg only. At this time she had a temporary right flexid hemiplegia and aphasia. The fits continued to recur in groups affecting sometimes right and left sides only. Subsequently she began to have frequent minor attacks of a kinetic type and she became abnormally tearful and fidgety. After a few weeks her behaviour at home became an acute problem and she was wilful and screaming with any frustration. Psychological tests at this time gave her provisional Binet I.Q. as 72. In spite of full doses of anticonvulsants the fits continued as did the mental deterioration and she had to be admitted at the age of 5 to an epileptic colony. For the next few years the fits diminished in number, and she then became free of fits for several years. By 1958 she was able to leave the colony and her I.Q. on testing was about 93. She was just able to hold her own in an ordinary school though still somewhat emotionally unstable.

The second case, D.L. born on January 26, 1943, had a normal birth and early development. At the ages of 2 years, 3½ years, and 4 years he had groups of fits but then the fits became much more frequent and he was admitted to the Maudsley Hospital at the age of 10 years. Up to this time he had managed to hold his own in an ordinary school but with increasing difficulties, especially as regards behaviour. He was discharged from the Maudsley to an epileptic colony, but his stay lasted only two months when his violent behaviour necessitated his admission to a remand home. An I.Q. test in 1951 gave a score of 93 on the W.I.S.C. but by 1954 the score had dropped to 80. E.E.G.s showed several epileptogenic areas, the most active of which was in the left temporal region. The A.E.G. was normal and there were no neurological signs except for a right homonymous hemianopia. A left temporal lobectomy of standard type was carried out on July 27, 1954. Following the operation his fits were controlled but for many months his behaviour remained difficult and his I.Q. test scores continued to fall. However, he was then sent to a special residential school for maladjusted children and began to make good progress so that by 1958 his I.Q. score had returned to 94 and he was able to go home and start a normal job free of fits. It is of interest that at this time his E.E.G. was relatively normal as regards background rhythms and absence of foci but he had a few bursts of generalized spikes and waves of centrencephalic type which have been in one or two other adult temporal lobectomy cases (Hill, personal communication).

The reversibility of mental change is in contrast to the lack of progress shown by infants with so-called hypsarrhythmia (Gibbs, Fleming, and Gibbs, 1954) or infantile spasm (Illingworth, 1955). This latter condition differs from the present series of cases in showing an earlier and simultaneous onset of fits and deterioration. Like the present series it is probably only a clinical syndrome with a variety of possible causes.

This investigation thus stressed the comparative unimportance of certain factors in the production of deterioration: the presumptive age of brain damage; the number of years fits have continued; the quantity of anticonvulsants and adverse social and psychological factors do not seem very important. On the other hand, the close correlation with the number of attacks and the apparent reversibility of deterioration when the attacks are brought under control would suggest that there may be some sort of 'subclinical' epilepsy which causes deterioration.

Such a concept has long been upheld by older authorities, and terms such as 'epileptic equivalent' or 'epileptoid psychopath' imply a similar mechanism. However, to be effective such discharges must be of a certain type or affect certain areas and not others, since, for example, patients with pure petit mal and frequent generalized symmetrical three-per-second spike and wave do not appear to suffer any ill effects from such discharges. Several authors have pointed out the resemblances between the behavioural disturbances and learning difficulties seen in epileptics and the effects in animals of epileptogenic lesions in the rhinencephalic regions or visceral brain loosely so-called.

It is probable that the patients in this series had lesions in these regions but so probably had some of the control cases and we are still ignorant of the reasons why some lesions seem so much more disturbing than others.

Summary

Twenty-eight epileptic children from the Maudsley and Fountain Hospitals who showed intellectual and social deterioration were compared with a control group of epileptics who had similar evidence of brain damage but no deterioration.

Significant differences were found in the increased frequency of seizures, the poor effects of medication on the seizures, and the incidence of focal plus generalized E.E.G. abnormalities in the cases.

Insignificant differences were found in the site and extent of brain damage, the presumptive age when the brain was damaged, the age of onset of seizures, the amount and duration of anticonvulsants, and the associated emotional and behavioural problems.

Attention is drawn to certain cases which improve after long periods of apparent deterioration and a hypothesis is put forward that some form of 'subclinical' epilepsy may be partly responsible for deterioration which is not a true dementia.

Our thanks are due to Dr. Hilliard and Dr. Kirman of the Fountain Hospital for their help and kindness in allowing us access to their patients.

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THE DIAGNOSTIC USE OF THE McGILL PICTURE ANOMALY TEST IN TEMPORAL LOBE EPILEPSY

BY

DENIS C. SHALMAN

From the Department of Psychology, Institute of Psychiatry, and the Guy's-Maudsley Neurosurgical Unit, Maudsley Hospital, London

In 1958, Milner applied the McGill picture anomaly test to patients with temporal lobe epilepsy and reported certain dysfunctions in patients with epileptic disturbances of the non-dominant hemisphere. This test had been prepared by Hebb and Morton (1943) and the results obtained from using it formed the basis for Hebb's (1939) conclusions regarding the defects that followed a right temporal lobectomy, namely, a disturbance of capacities not concerned with language. Precisely what the test measures is not known, but Milner suggests that, in addition to the trait which Hebb mentions, it involves pictorial comprehension and visual identification, and it is these functions that she attributes to the right temporal lobe. Dr. Milner reported her observations on 50 subjects with lesions in the temporal lobe.

A systematic investigation has been carried out at the Guy's-Maudsley Neurosurgical Unit to determine validity of the McGill picture anomaly series as a diagnostic tool.

Subjects

The 21 subjects were patients of the Guy's-Maudsley Neurosurgical Unit. Every epileptic patient admitted to the unit for temporal lobectomy over the past two years was included in the sample, and this was the only selection factor. All were tested before and one month after a unilateral anterior temporal lobectomy of about 6 to 7 cm. extent. The resection (performed by Mr. Murray A. Falconer) included the mesial structures, consisting of the hippocampus, uncus, and amygdaloid nucleus, and extended on the surface backwards to Labbe's vein. The decision as to which side was operated was made largely on E.E.G. criteria (Falconer, Hill, Meyer, Mitchell, and Pond, 1955).

Tests

The McGill picture anomaly test (Hebb and Morton, 1943) consists of two highly correlated forms ($r = 0{\cdot}93$) each containing a total of 34 pictures, each of which has some incongruous feature. The test is not a verbal one, the instructions, ('show me what is funny or out of place') being kept to a minimum. The subject must identify the anomaly by pointing, and the correctness of the response and the time scores are recorded. All patients received Form M before operation and Form N after the lobectomy.

The untimed version of the progressive matrices (Raven, 1938), a non-verbal test of intelligence, was used to assess the level of cognitive functioning independent of the speed of performance. Form I of the Wechsler-Bellevue intelligence scale was also administered preoperatively.

Results

The patients were divided into three groups: (1) Right-handed patients with a left temporal lobectomy; (2) right-handed patients with a right temporal lobectomy; (3) left-handed patients with a lobectomy on either right or left side. The groups have been equated for age, sex, and the full-scale I.Q. (Table I) and it can therefore be assumed that they form a homogeneous sample. Only patients

TABLE I

OPERATIVE GROUPING

	Right-handed Patients with Left Temporal Resection		Right-handed Patients with Right Temporal Resection		Left-handed Patients with Resection of Either Hemisphere	
Number	6 (3 M, 3 F)		10 (5 M, 5 F)		5 (2 M, 3 F)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age	34·5	9·4	27·1	9·1	32·4	10·6
Full-scale I.Q.	103·8	9·9	104·6	12·9	103·4	14·9
Verbal scale I.Q.	103·1	10·3	103·1	12·7	105·6	12·4
Performance scale I.Q.	103·0	9·7	105·6	11·9	99·6	19·5

TABLE II

RESULTS OF McGILL PICTURE ANOMALY TEST WITH ERROR AND TIME SCORE BEFORE AND AFTER UNILATERAL LOBECTOMY

	Right-handed Patients with Left Temporal Resection		Right-handed Patients with Right Temporal Resection		Left-handed Patients with Resection of Either Hemisphere	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Error						
Pre-operative	8·3	4·1	8·3	3·9	10·0	2·8
Post-operative	11·3	5·2	11·0	5·4	11·0	2·3
Time						
Pre-operative	8·5	2·7	9·4	3·5	12·1	4·4
Post-operative	9·7	2·6	10·6	2·7	10·5	2·1

TABLE III

PRE-OPERATIVE SCORES ON RAVEN'S PROGRESSIVE MATRICES AND ON FULL-SCALE I.Q. OF WECHSLER-BELLEVUE INTELLIGENCE SCALE

	Right-handed Patients with Left Temporal Resection		Right-handed Patients with Right Temporal Resection		Left-handed Patients with Resection of Either Hemisphere	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Full scale	103·8	9·9	104·6	12·9	103·4	14·9
Progressive matrices	107·3	12·3	96·2	4·5	114·0	10·2

with an abnormality in one temporal lobe, as determined by pre-operative electroencephalography, are included in this study (Falconer *et al.*, 1955). The discrepancy between the verbal and performance scale scores is not significant for either the left temporal lobe or the right temporal lobe group.

Analysis of the McGill picture anomaly test indicates that neither error nor time scores differentiate the left temporal from the right temporal lobe groups on pre-operative testing (Table II). On post-operative testing, both groups were found to increase their error scores to the same extent, and thus they cannot be differentiated on this basis. Furthermore, no increase in time scores was manifested on post-operative testing, and so this measure also fails to discriminate between the groups.

As can be seen from Table II, there were five left-handed patients with resections of one or the other temporal lobe. This left-handed group had slightly higher error scores than either of the right-handed groups before lobectomy, but the difference is not statistically significant. The time scores for the left-handed group were significantly higher ($P < 0{\cdot}01$) than for both the right-handed groups before surgery, but the post-operative results were not significant. The results obtained from this small sample tend to differentiate the left-handers as a group from the right-handers. A similar conclusion is reached when the discrepancy between the verbal and performance scores are examined (Table I); only the left-handed group showed a performance score lower than the verbal score, but the difference was slight.

The left-handed group is admittedly small. However, they score significantly differently from right-handed patients on some tests and for this reason have been classified separately. The method of selecting handedness was determined by hand preference for everyday tasks excluding writing. In only one patient was an attempt made to relate handedness to cerebral dominance. This was done by a bilateral intracarotid injection of sodium amytal and in this instance dysphasia was produced by the left intracarotid injection (Wada and Rasmussen, 1960). It might be argued that some of the group were 'converted sinistrals' but there is no evidence to suggest this. Since the contralateral hemisphere is speech dominant in only half of the cases in left-handed patients (Humphrey and Zangwill, 1952), and because of the incomplete history on the handedness of the patients and their ancestors, it was decided to treat them as a separate group.

Analysis of the intelligence test scores (Table III) indicates that patients with disturbance of the right temporal lobe score significantly lower ($P < 0{\cdot}01$) on the matrices than on the Wechsler tests. Patients who subsequently underwent a left temporal lobectomy scored slightly higher on the matrices than on the Wechsler tests, but this does not achieve an acceptable level of significance.

Discussion

These results on the McGill picture anomaly test do not support the prediction that patients with abnormalities in the right temporal lobe will be inferior on error and time scores to the left temporal lobe group. Contrary to Milner's prediction, the time scores did not increase significantly following lobectomy on either side. Furthermore, increases in error score were the same for both groups. Thus

Milner's results are not supported in our somewhat smaller sample, and this casts doubt on the assumption that the test has a diagnostic value of the kind suggested by Milner.

It might, of course, be argued that cultural influences between North American and British patients could have masked real differences of the kind which Milner predicted, but this seems unlikely. It may, however, be appropriate to note that patients are referred to the Montreal Unit mainly for epileptic symptoms, whereas patients at the Guy's-Maudsley Unit probably offer a greater incidence of psychiatric disorders.

Milner does not comment upon the relationship between the right and left temporal lobe groups on the McGill picture anomaly test and only briefly mentions that 'the right temporal lobe patients make significantly more errors ($P < 0{\cdot}01$) both before and after the operation than other brain-injured subjects'. She does not elaborate on the category of 'brain-injured subjects', and it seems likely that this was a heterogeneous group with widespread lesions involving the frontal and parietal regions which could cause a marked degree of skewness to the results. It would seem reasonable that when a particular function is credited to the right temporal lobe it is necessary to show that the left temporal lobe is not involved to the same degree.

When discussing the Wechsler-Bellevue scale, Milner stresses the inferior performance of patients with right temporal lobe lesions on non-verbal tests, and cites the decline of the scores on the performance scale as evidence. This particular finding was not confirmed in the present investigation. However, it seems possible that if this were true it could account for the results on the McGill picture anomaly test; the non-verbal element is common to both tests and seems to be the most likely differentiator of right temporal and left temporal lobe cases.

Raven's progressive matrices is an excellent non-verbal intelligence test and correlates highly with the Wechsler-Bellevue test (Hall, 1957). The progressive matrices test was included pre-operatively to assess the importance of the non-verbal factor, and analysis indicates ($P < 0{\cdot}01$) that the test discriminates not only the right from the left temporal lobe (in right-handed subjects) but also the left-handed group from the right-handed group. It appears, therefore, that its non-verbal nature is important; or, as Hebb (1939) originally stated, 'the removal from the right temporal lobe was followed by a disturbance of non-language capacities'.

Left-handed patients are seldom reported in the literature, and since little is known about the neuro-anatomical and physiological relationships of this group, it has usually been set aside and not considered in psychological studies. However, for the tests employed on this occasion, it was the only group to demonstrate significant differences for laterality of lesion and operative interference. Conclusions on this group must remain tentative, but it appears that the group is more resistant to detrimental effects produced by a temporal lobectomy. More will be said about this group in a later publication.

Summary and Conclusions

An analysis of the McGill picture anomaly test suggests that its use as a diagnostic test for laterality of a lesion in temporal lobe epileptics is not supported. Contrary to Milner's (1958) predictions the test did not differentiate patients with right temporal lobe disorders from patients with left temporal lobe disorders. Possibly the observations of Milner can be accounted for in terms of the right temporal lobe being important for performance on non-verbal tasks. The progressive matrices test was included to assess this supposition, and it discriminated at a high level of significance between patients with disorders in the right temporal lobe and patients with the left temporal lobe involved. Left-handed patients, as a group, tended to obtain scores significantly different from right-handed patients on the psychometric tests both pre-operatively and post-operatively.

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HISTOLOGICAL AND CHEMICAL FINDINGS IN KRABBE'S LEUCODYSTROPHY

BY

R. M. NORMAN, D. R. OPPENHEIMER, and A. H. TINGEY

From the Burden Neuropathological Laboratory, Frenchay Hospital, Bristol, and the Department of Neuropathology, the Radcliffe Infirmary, Oxford

The familial disease of the cerebral white matter named after Krabbe (1916) may be distinguished histologically from other leucoencephalopathies of early life by the presence of conspicuous nests of macrophage cells, some of large size with several peripherally placed nuclei, lying closely packed around the smaller vessels of the cerebral white matter. The large multinucleated cells were designated 'globoid cells' by Collier and Greenfield (1924), and Greenfield (1958) later gave the name 'epithelioid' to smaller mononuclear cells which also help to form the perivascular packets. Both types of cell contain a substance having the histochemical properties of a glycolipid bound to protein (Diezel, 1955; Stammler, 1956). Since mononuclear, or sometimes multinuclear, cells containing complex lipid material may be present in other types of diffuse sclerosis (Ferraro, 1927; Seitelberger, 1960), it is necessary to stress in the definition of Krabbe's disease this relationship of the cell packets to the smaller vessels. If this criterion is applied, there are some 25 recorded cases of this disorder (Hallervorden, 1957), all of which concerned children dying before the age of 7 years. There are also two, more doubtful, sporadic cases which have been described in adults (Verhaart, 1931; Guillain, Bertrand, and Gruner, 1941). This list includes the earliest case on record, that of Bullard and Southard (1906), who described typical neuropathological findings in a boy dying at the age of 6½ years after an illness lasting one year.

There has been much speculation as to the origin and function of the globoid cells, whether they are formed by microglia engaged in engulfing and transporting products of myelin breakdown to the vessels, or whether they are derived from the vascular adventitia and, if so, whether their abnormal lipid content is a phenomenon of primary storage, as in a lipidosis. The recent observations of Stammler (1956) strongly suggest that the perivascular globoid and mononuclear cells are both adventitial derivatives and our cases throw further light on this important feature.

The histological observations on these cases have been supplemented by chemical analysis of the cerebral cortex and white matter, using a method by which neutral or true cerebroside may be separated from other glycolipids. We have found this to be present in relatively normal amount despite the severe degeneration of the white matter and a substantial loss of other myelin lipids.

Case Reports

Case 1.—A boy aged 9 months at death was the second child, an elder sibling being healthy. The parents were normal and not blood relations. He was born at full term and weighed 7½ lb. Progress was normal until the sixth month when feeding became difficult and the legs were noted to be stiff. On admission to hospital two weeks later, he showed head retraction, marked spasticity of the limbs, and extensor plantar responses. The optic discs were slightly pale but he appeared alert and could follow objects with his eyes. A ventriculogram showed slight dilatation of the frontal horns and much subdural air. Examination of the cerebrospinal lumbar fluid showed no cells, protein 270 mg. per 100 ml.; fluid from the right ventricle, 40 cells, 170 mg. of protein per 100 ml., and from the left ventricle 3 cells, 170 mg. protein per 100 ml. A radiograph of the spine showed unfused neural arches down to D9. During the last months of life a steady deterioration ensued. Muscle tone varied but the usual posture was one of opisthotonus. Death followed an attack of bronchopneumonia.

Case 2.—A girl aged 6 months at death was the younger sister of the first patient (Case 1). Birth was normal and the birth weight 8¼ lb. She appeared to be developing normally until the age of 3 months, when jerky movements were noticed in the arms and legs and she became difficult to feed. On admission to hospital at the age of 4 months, she was found to be an irritable child with a high-pitched cry. The limbs jerked frequently. There was no spasticity at this stage. The plantar responses were extensor. Lumbar puncture yielded a slightly blood-stained fluid with a protein of 340 mg. per 100 ml. Tests for toxoplasmosis were negative. There was no

abnormal aminoaciduria on chromatography. During the next weeks she developed a generalized spasticity and became opisthotonic. She had increasing difficulty in swallowing and death occurred after a respiratory infection.

Case 3.—A boy aged 13 months at death was the first-born child of healthy parents who were not blood relations. He was born by forceps delivery owing to foetal distress, but appeared to make normal progress until he was about 2 months old, when vomiting and feeding difficulties began and the legs were noted to be stiff. At the age of 6 months he was found to be about three months retarded in his motor and adaptive behaviour (Griffiths mental development scale). Progressive mental deterioration and spasticity developed and death occurred from bulbar paralysis. Shortly before death the blood of the child and mother were examined for toxoplasmosis with negative results.

Examination of the Central Nervous System

With certain exceptions to be noted later the pathological features of these brains were closely similar and will be described together to give a composite picture.

Macroscopic.—Brain weights (unfixed) were in Case 1, 666 g., in Case 2, 616 g. The meninges and convolutional pattern were not remarkable. In Case 2 the optic nerves were unduly large. On section, the lateral and third ventricles were slightly enlarged. The white matter of the cerebral hemispheres was tough and greyish except for the subcortical U fibres of Cases 1 and 3 which appeared to be preserved. The cerebellar white matter was sclerosed and in Case 3 the folia were slightly shrunken, especially on the dorsal surface. The brain-stem and spinal cord were also firmer in consistency than the normal and in Case 3 the distinction between grey and white matter was obscured. Prominent lateral sulci were present in the spinal cords.

Microscopic.—Representative blocks were examined in celloidin, paraffin and frozen sections, stains for nerve cells, axis cylinders, myelin, fibrous neuroglia, lipid and carbohydrate being employed.

Changes in White Matter.—Frozen sections stained by Kultschitsky-Pal revealed a severe loss of myelinated fibres in the cerebral and cerebellar white matter (Figs. 1 and 2). In Case 3 virtually the whole of the centrum ovale was affected, though the U fibres were well preserved. In Case 2 the U fibres were not so strikingly spared (Fig. 3). In Case 1 the loss was most marked in the central regions of the hemispheres, and the occipital lobe was relatively well myelinated except for the optic radiation and periventricular fibres (Fig. 5).

In the basal ganglia a diffuse but incomplete loss of fibres was seen in the thalamus. The globus pallidus in Cases 1 and 2 was similarly affected, but in Case 3 the changes were more patchy. The striatum in Cases 1 and 2 was almost devoid of fibres, but in Case 3 the compact bundles in the putamen were remarkably preserved (Fig. 6). The internal capsule was severely damaged in all cases, while the optic tracts retained some of their peripheral fibres (Fig. 6). The mammillothalamic fasciculus and the stria medullaris were well myelinated.

In the brain-stem the cerebral peduncles (Fig. 7) and pyramids had completely degenerated, and the latter contained small cavities in Cases 2 and 3. The restiform body, the transverse fibres of the pons, the medial lemniscus and inferior olivary fibres, were well preserved in Case 1 only.

The superior cerebellar peduncles were severely affected. There was a striking preservation of the intramedullary portions of the cranial nerves, and of the medial longitudinal bundles.

Myelination of the spinal cord was poor throughout, particularly in Case 2. The posterior columns in general were less affected than other tracts. The pyramidal tracts were severely damaged, while elsewhere the fibre loss was diffuse and incomplete.

Loss of axis cylinders generally went hand in hand with demyelination, though it was noted that considerable numbers of fibres remained in the severely demyelinated internal capsules and optic nerves.

A fibrous gliosis of remarkable density was present throughout the entire white matter, reaching its maximum in the fully degenerated areas (Figs. 4 and 8). In the latter situations the cellular proliferation was also extremely marked, the astrocytic nuclei being unusually large and pleomorphic. The cell bodies were swollen and stained faintly with the periodic-acid-Schiff (P.A.S.) method. Oligodendroglia had largely disappeared from the sclerosed areas but was present in less affected parts of the white matter.

Microglial cells, many with swollen processes staining pink with P.A.S., were numerous in the U fibres and less affected areas of the cerebral white matter. In Case 2 the corpus callosum and pillars of the fornix contained large aggregations of microglial cells showing droplets of neutral fat and doubly refractile lipid in their processes, but fully formed fat-granule cells were rare. The scarlet-staining lipid occasionally seen in the walls of vessels in the white substance was mainly in the form of extracellular droplets.

Globoid and epithelioid cell packets were a characteristic feature of all cases (Fig. 9 to 11). The former were large round cells, 20-40μ in diameter, with several peripherally placed, oval nuclei (Fig. 12). Their homogeneous cytoplasm stained pink with

FIG. 1

FIG. 3

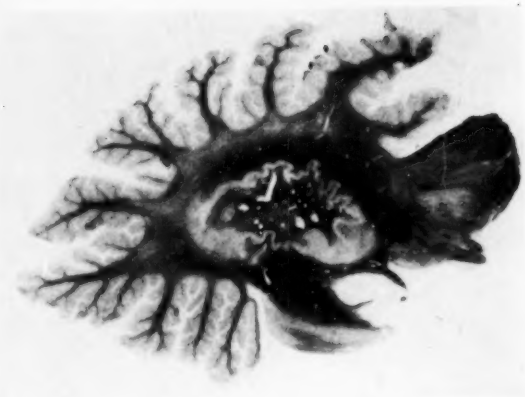

FIG. 2

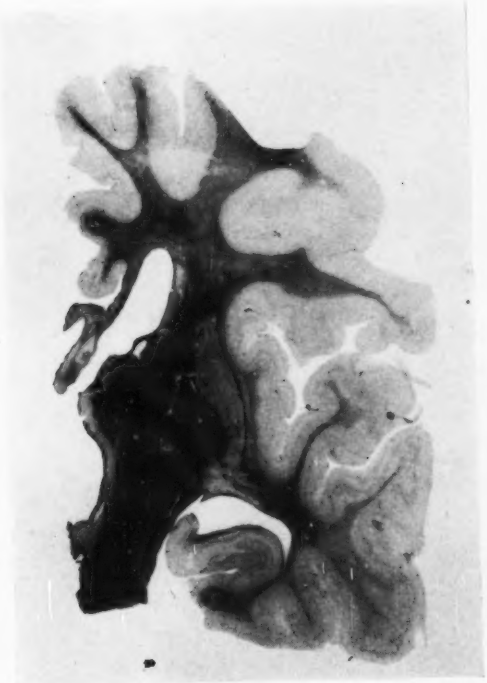

FIG. 4

FIG. 1.—Case 3. Myelinated axons in the centrum ovale have almost completely disappeared. The U fibres are preserved. Kultschitsky-Pal × 3.

FIG. 2.—Case 1. The cerebellar white matter shows diffuse demyelination. Myelinated fibres in the dentate nucleus are completely lost. Kultschitsky-Pal × 1·5.

FIG. 3.—Case 2. Diffuse demyelination of centrum ovale with but little relative preservation of the U fibres. Kultschitsky-Pal × 0·9.

FIG. 4.—Case 2. Corresponding section to Fig. 3. Dense fibrous gliosis in the centrum ovale, thalamus, globus pallidus, and cerebral peduncle. Holzer × 0·9.

FIG. 5

FIG. 6

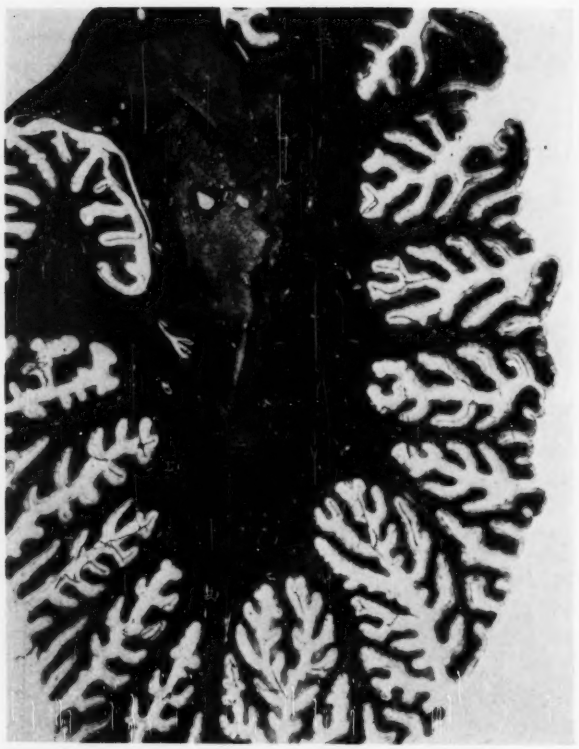

FIG. 8

FIG. 7

FIG. 5.—Case 1. Occipital lobe showing loss of myelinated fibres in the optic radiation and periventricular region. Kultschitsky-Pal × 1·4.

FIG. 6.—Case 3. Basal ganglia. There is severe loss of myelinated fibres in the internal capsule, cerebral peduncle, and lateral thalamic nucleus. The optic tract and globus pallidus are less affected. The putamen is well preserved. Kultschitsky-Pal × 3·2.

FIG. 7.—Case 1. Midbrain showing severe loss of myelinated fibres in the cerebral peduncles, substantia nigra, and red nuclei. Kultschitsky-Pal × 2.

FIG. 8.—Case 3. Intense fibrous gliosis in the severely demyelinated cerebellar white matter and dentate nucleus. Holzer × 3·2.

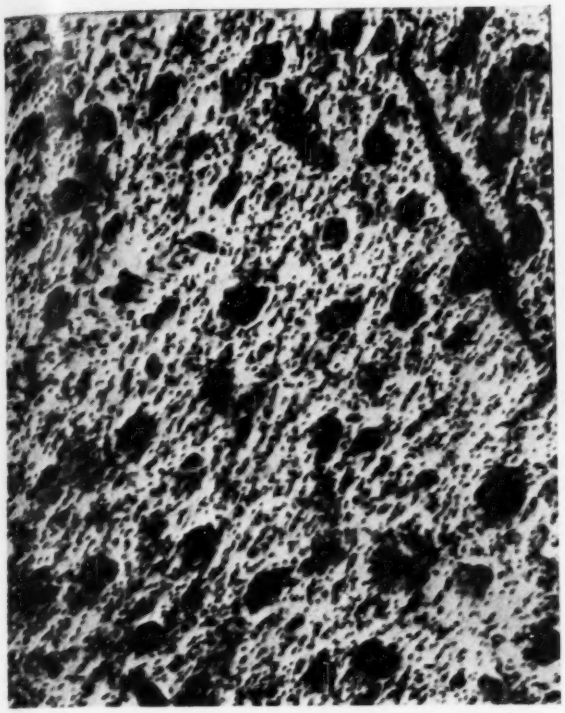

FIG. 9

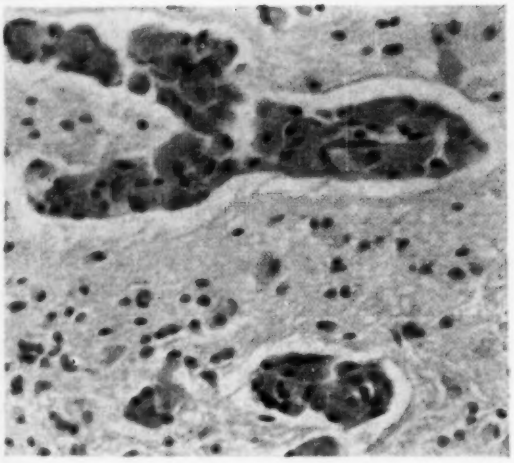

FIG. 10

FIG. 9.—Case 2. The degenerated cerebral white matter contains numerous packets of globoid and epithelioid cells. Carbol azure × 74.

FIG. 10.—Case 3. Typical cell packets around small vessels in the white matter. P.A.S. and haematoxylin × 190.

FIG. 11.—Case 3. Packet containing one globoid and several epithelioid cells. P.A.S. and haematoxylin × 480.

FIG. 12.—Case 1. Large globoid cell. P.A.S. and haematoxylin × 1,230.

FIG. 13.—Case 1. The corpus callosum contains an area of tumour-like cell density. P.A.S. and haematoxylin × 35.

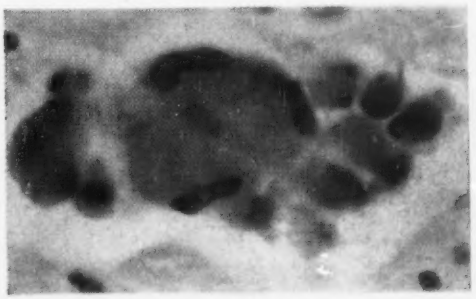

FIG. 11

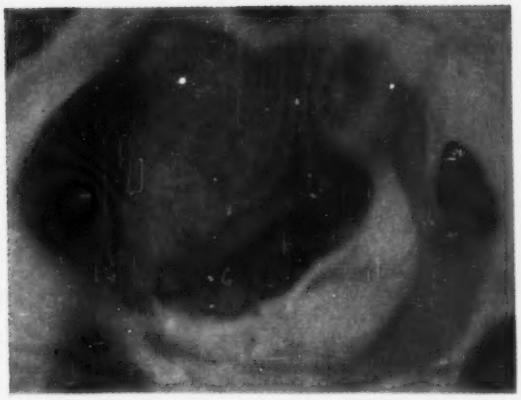

FIG. 12

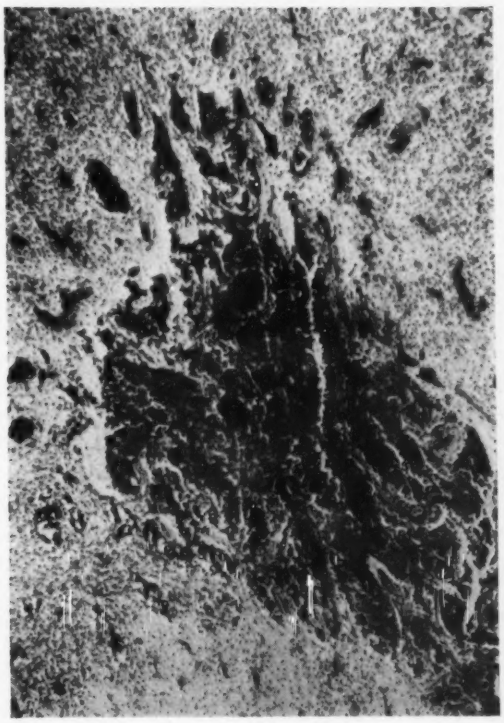

FIG. 13

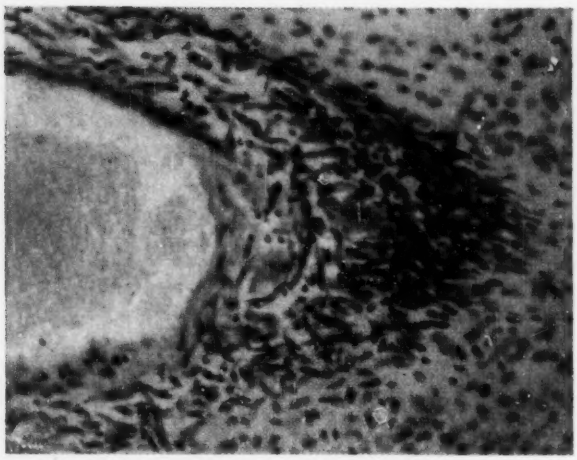

FIG. 14

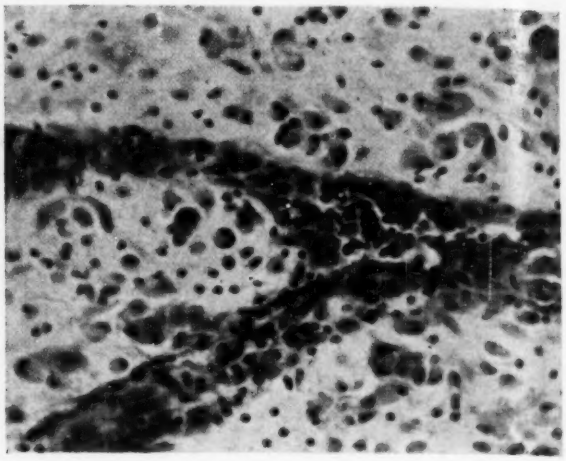

FIG. 15

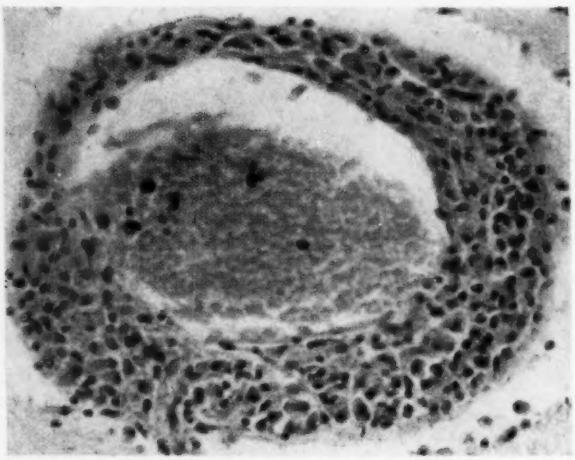

FIG. 16

FIG. 14.—Case 1. Spindle-shaped adventitial cells of a large vein in the cerebellar white matter, containing crimson granules. P.A.S. and haematoxylin × 190.

FIG. 15.—Case 1. Small vessel in frontal white matter, showing crimson material in adventitial cells and pink material in globoid and epithelioid cells. P.A.S. and haematoxylin × 190.

FIG. 16.—Case 3. A dense cuff of lipid-laden mononuclear cells surrounding a vein of the central white matter. P.A.S. and haematoxylin × 190.

P.A.S. and grey with Sudan black, and was unaffected by lipid solvents. Smaller mononuclear cells corresponding to Greenfield's (1958) definition of epithelioid cells were also found within the packets. These cell packets were centred only around the smaller vessels, usually precapillaries, the scanty reticulin fibrils of which were confined to the vessel wall and did not surround the globoid cells. The cell packets were not uniformly distributed throughout the degenerated white matter and were often absent from large areas, though isolated mononuclear and multinucleated cells were diffusely scattered throughout the tissues. The corpus callosum in Case 1 included an area in which globoid and epithelioid cells, together with swollen astrocytes and microglia, formed a dense, tumour-like, cellular mass (Fig. 13). Globoid cells were not found within the Virchow-Robin spaces of the larger vessels.

There was a remarkable difference in our cases in regard to the type of cells present in the outer coats of the larger vessels of the white matter. In Cases 1 and 2, but not in Case 3, many of the veins showed a thickening of the adventitial coat due to the presence of numerous spindle-shaped cells filled with granules staining a brilliant crimson with P.A.S. (Figs. 14 and 15). This intense colour was never seen in the globoid, epithelioid, or microglia cells of the white matter. No transition could be traced between these bipolar cells and epithelioid cells. On the other hand, in Case 3, the veins of the cerebral and cerebellar centre were usually surrounded by dense cuffs of exclusively mononuclear cells which resembled in their form and staining reactions the epithelioid cells of the cell packets (Fig. 16). Unlike the latter, these closely packed mononuclear cells were enclosed by reticulin fibrils and were sharply separated by them from the surrounding tissue. No granular spindle-shaped cells were seen in any vessel of Case 3, nor were the dense perivascular aggregations of round cells found in the first two cases.

Changes in Grey Matter.—The cerebral cortex appeared to be normal as regards arrangement and number of nerve cells. Myelination of the radial bundles was extremely poor and the supraradial fibres were not demonstrable.

In the thalamus nerve cells had disappeared except in the nuclei of the midline. This was accompanied by an intense fibrillary and cellular gliosis.

The small nerve cells of the caudate nucleus and putamen in Cases 1 and 2 and the caudate nucleus of Case 3 were severely depleted and large fibrous astrocytes were present in the grey matter. In Case 2 abundant droplets of neutral fat were present in the caudate nucleus and globus pallidus.

The brain-stem nuclei were intact except for severe degeneration of the inferior olives in Cases 2 and 3.

The cerebellar cortex in Cases 1 and 2 appeared normal except for a mild proliferation of the Bergmann fibrils and the presence of fat-laden microglial cells in the molecular layer. In Case 3, however, the gliosis was intense and the granular layer rarefied, particularly in the vermis. Many folia also showed a loss of Purkinje cells, some of the survivors having axonal and dendritic swellings. In all cases the dentate nuclei had almost completely degenerated.

The nerve cells of the spinal cord showed no significant change.

Strongly P.A.S.-positive granules were seen in the adventitial fibroblasts of the vessels in many parts of the grey matter (Cases 1 and 2 only). These changes were very conspicuous in the thalamus, and less marked in the cerebral cortex, granular layer of the cerebellum, corpus striatum, brain-stem, and spinal cord.

Meninges.—In celloidin sections from Case 1 a few of the arachnoidal cells were seen to contain strongly P.A.S.-positive granules.

Eye (Case 2).—Except for a marked loss of ganglion cells the retina appeared normal. A few glial cells containing P.A.S.-positive granules were seen near the optic disc in the superficial part of the nerve fibre layer.

Visceral Organs.—Histological examination in Case 2 of heart, liver, kidneys, pancreas, spleen, lymph node, bone marrow, pituitary, adrenal, thyroid, and ovary revealed no abnormality. The lung showed the changes of bronchopneumonia and no multinucleated cells were found.

Chemistry

Methods.—Total lipid hexose was estimated by the method of Mallov, McKibbin, and Robb (1953). Neutral hexose was estimated by a modification of the technique of Radin, Lavin, and Brown (1955). By this method the acid carbohydrate lipids, namely, ganglioside and cerebron sulphuric acid, are separated from the neutral carbohydrate lipids (cerebroside). Lipid extracts obtained by hot extraction with 2 $CHCl_3$: 1 MeOH were used, extraction with acetone being omitted. The dried cerebroside was hydrolysed and the hexose estimated by the method of Mallov *et al.* (1953). Lipid sulphur was estimated by a modification of the method of Cuthbertson and Tompsett (1931). The lipid extract was ashed with HNO_3 and a small amount of NaCl, the ash taken up in 4% trichloracetic acid and the precipitated sulphur estimated colorimetrically. More than 10 μg. S. must be taken for the precipitation to be complete (Dodgson and Spencer, 1953), and the aliquot taken for colorimetric estimation should contain about 2 μg. S. Hexosamine, neuraminic acid, and other substances analysed were estimated by methods cited in previous papers (Tingey, 1956, 1959). Sphingomyelin was assessed by difference of the choline fractions and does not include cephalin B.

Time in Formalin.—The brains from Cases 1 and 3 had been fixed in 10% formol saline for two weeks and 10 months respectively before analysis was started. The brain from Case 2 was obtained unfixed. Control material consisted of two normal brains of infants dying at 9 months, one unfixed, the other fixed in formalin for approximately 12 months. Use has also been made of a normal brain of a child of 12 months which had been fixed in formalin for about a year.

Results

Glycolipids.—In the white matter the neutral hexose has remained at a surprisingly high figure compared with the normal, while in the cerebral cortex it shows an absolute increase over normal (Table I). In the fresh brain (Case 2) both the lipid

TABLE I

GLYCOLIPIDS

	Normal (9 months) Formalin	Case 1 (9 months) Formalin	Case 2 (6 months) Fresh	Case 3 (13 months) Formalin
Total lipid hexose (g./100 g. dry tissue)	1·85 (1·03)†	1·51 (1·29)	1·26 (0·97)	0·85 (0·56)
Neutral hexose (g./100 g. dry tissue)	0·75 (0·20)	0·86 (0·44)	0·68 (0·36)	0·66 (0·36)
Lipid hexosamine (g./100 g. dry tissue)	0·077 (0·172)	0·055 (0·121)	0·137 (0·148)	0·077 (0·146)
Neuraminic acid (g./100 g. dry tissue)	0·132* (0·483)	0·106 (0·384)	0·286 (0·426)	0·181 (0·392)
Lipid sulphur (g./100 g. dry tissue)	0·117 (0·093)	0·059 (0·083)	0·082 (0·046)	0·038 (0·028)

†Figures for cerebral cortex are in brackets. Asterisk indicates 1 year control.

hexosamine and the neuraminic acid are substantially increased in the white matter. The lipid sulphur is reduced in the white matter of Cases 1 and 3 and in the cortex of Cases 2 and 3.

Phospholipids.—Owing to the well-recognized effect of formalin upon phosphatides, only the results obtained from unfixed material have been included in Table II. The sphingomyelin in the white matter is reduced by a half compared with the normal. The lecithin is not affected. The sphingomyelin of Cases 2 and 3 (not in Table II) also showed a similar reduction in the white matter (0·8 and 0·9 respectively).

TABLE II
PHOSPHOLIPID

	Normal (9 Months) Fresh	Case 2 (6 Months) Fresh
Total phospholipid (g./100 g. dry tissue)	20·7 (19·5)†	15·0 (19·7)
Lecithin (g./100 g. dry tissue)	8·2 (7·8)	7·6 (10·7)
Sphingomyelin (g./100 g. dry tissue)	1·7 (1·0)	0·8 (0·3)

†Figures for cerebral cortex are in brackets.

Other Estimations.—The free cholesterol is reduced in the white matter of the three cases (Table III). No appreciable change is present in ester cholesterol. In Cases 1 and 2 there is an increase in the non-lipid hexosamine in both the white and grey matter. In the fresh brain (Case 2) there is a four-fold increase in the water-soluble hexosamine of the white matter.

in that the loss of myelinated axons tends to be widespread throughout the central nervous system and is particularly severe in the cerebrum, the cerebellum, and the cortical projection fibres. From the chemical standpoint the leucodystrophies also differ from true demyelinating diseases in their raised level of lipid hexosamine, a peculiarity which they share with certain lipidoses (Edgar, 1957).

It has already been pointed out that the pathognomonic histological feature of Krabbe's disease is the presence of packets of globoid and epithelioid cells around the smaller cerebral vessels in the degenerated white matter, but the final classification of this disease will doubtless depend upon the identification of the predominant chemical abnormality. Histochemical studies (Diezel, 1955; Stammler, 1956) have suggested that the macrophage cells, whether perivascular or diffusely scattered, contain a substance having the properties of a cerebroside bound to protein. Chemical analysis of brains in this disease has not, however, given uniform results.

A reduction in the amount of cerebroside was reported by Klenk in one of Hübner and Hallervorden's (1956) cases and by Brante in the case of Kaijser and Lundquist (1948). In the chemical analyses of seven other cases of Krabbe's disease recorded by Cumings (1960), only the 'galactose cerebroside' (calculated from the total lipid hexose) was estimated. This was found to be substantially increased in both cortex and white matter in the

TABLE III
OTHER ESTIMATIONS

	Normal (9 Months) Formalin	Normal (9 Months) Fresh	Case 1 (9 Months) Formalin	Case 2 (6 Months) Fresh	Case 3 (13 Months) Formalin
Total lipid (g./100 g. dry tissue)	42·0	46·3 (33·0)	31·4 (30·8)	41·0 (38·4)	26·4 (32·0)
Free cholesterol (g./100 g. dry tissue)	8·4 (5·1)†	11·0 (5·8)	4·0 (3·2)	6·4 (5·5)	5·3 (5·4)
Ester cholesterol (g./100 g. dry tissue)	nil (nil)	0·5 (nil)	0·3 (nil)	0·5 (nil)	nil (nil)
Non-lipid hexosamine (g./100 g. dry tissue)	0·333 (0·358)	(0·383)	0·455 (0·429)	0·523 (0·602)	(0·33) (0·414)
Water-soluble hexosamine (g./100 g. dry tissue)		0·034 (0·052)		0·122 (0·090)	
Water	72·4* (86·6)*	79·2 (85·5)	82·4 (87·8)	84·7 (87·9)	85·8 (73·2)

†Figures for cerebral cortex are in brackets. Asterisk indicates one-year control.

Discussion

In their main clinical and histological features these cases conform to other reported examples of Krabbe's disease. This condition is a leucodystrophy, a term originally introduced by Bielschowsky and Henneberg (1928) to signify an inherited disease of the white matter, in which the predominant products of abnormal myelin metabolism are not the usual scarlet-staining lipids found in disseminated sclerosis or Schilder's disease. Krabbe's disease also conforms to the topographical criteria of a leucodystrophy set out by Poser and van Bogaert (1956), 3-year-old case of Blackwood and Cumings (1954) but in the six younger patients the cerebroside levels were considered by Cumings to be normal. In our own Case 3 the 'galactose cerebroside' was markedly reduced in the white matter, yet the neutral cerebroside fraction still remained at an almost normal level. This finding suggests that neutral cerebroside is the glycolipid which tends to be selectively retained in the diseased tissues. In normal brains neutral cerebroside increases steadily with chronological age during early childhood and appears to be a better index of myelination than the total lipid

TABLE IV
NEUTRAL AND TOTAL HEXOSE IN NORMAL WHITE MATTER

	Neonatal	3 Months	9 months	12 months	2½ Years	4 Years
Neutral hexose (g./100 g. dry tissue)	0·33	0.49	0·75	1·25	1·53	2·37
Total lipid hexose (g./100 g. dry tissue)	1·05	2·10	1·85	2·10	2·43	3·60

hexose (Table IV). In metachromatic leucoencephalopathy we have found a reduction in this substance (Norman, Urich, and Tingey, 1960). Thus in the present cases of Krabbe's diseases there is the paradox of a centrum ovale grossly deficient in stainable myelin yet containing neutral cerebroside in relatively large amounts.

A central problem of Krabbe's disease is the derivation of the distinctive globoid cell packets. Such formations are not found in any other type of demyelinating disease or leucodystrophy. If globoid cells are derived from the microglia, as Blackwood and Cumings (1954) believe, it is strange that they should be centred almost exclusively around the smaller vessels, usually those of precapillary size. Blackwood (1954) and Blackwood and Cumings (1954) described in their case extracellular masses of P.A.S.-positive material, and the silver impregnation preparations suggested that these masses became engulfed by marginal microglial cells and eventually turned into globoid giant cells. We saw no extracellular material of this sort in our cases, and Peiffer (1957) has suggested that when free masses of 'cerebroside' are seen in this condition they are merely tangentially cut globoid cells. Opinion seems now to favour the view that these cells are derived from the vascular adventitia (Hallervorden, 1957; Diezel, 1955; Stammler, 1956; Greenfield, 1958). Hallervorden (1948) was struck by the resemblance between globoid and Gaucher cells, and it is well established that in the infantile form of the latter disease the adventitial cells of blood vessels in the cerebral white matter store a cerebroside-like substance (Norman, Urich, and Lloyd, 1956). Diezel (1956) believes that in Krabbe's disease 'the globoid cells have secondarily absorbed the glycolipids from the decomposed myelin sheaths, whereas the cerebrosides in the Gaucher cells arise primarily as a result of a cellular enzymatically caused metabolic disturbance'. Recent experiments by Austin, Leyfeldt, and Maxwell (1961) have given some support to this view. In a personal communication Austin states that cells closely resembling globoid and epithelioid cells were produced in the white matter of rats by the intracerebral injection of both natural and synthetic cerebrosides, and not by other lipids such as ganglioside, sphingomyelin, sulphatides, or cholesterol. Austin points out that these experimental findings cannot in themselves establish that human globoid cells arise as a specific reaction to the presence of cerebrosides. Nevertheless, it would seem that a pathogenetic factor of considerable importance has been disclosed.

A similar problem of interpretation was raised in our first two cases by the peculiar adventitial cell changes in the larger vessels of the white matter. Numerous spindle-shaped, fibroblastic cells contained granules staining much more intensely with the periodic-acid-Schiff method than the globoid or macrophage cells found elsewhere in the same brain. Stammler (1956) also discovered very marked proliferation of the adventitia of the larger vessels in his case of Krabbe's disease, and favoured the explanation that this was a response to the products of myelin breakdown, rather than a primary storage of cerebroside, as in a true lipidosis. Yet in other leucodystrophies and demyelinating diseases, in which cerebroside is present in the tissues either as a product of myelin breakdown or of defective anabolism, vascular reactions of these types are not found. It appears to us that the possibility cannot be ruled out that in Krabbe's disease there may be some additional or perhaps variable abnormality in the adventitial cells themselves, owing to which cerebroside is hindered in its passage through the vessel walls into the blood stream. Such a factor would account for the variation in the number of globoid cells present in different fields in the same brain and for the variable type of adventitial reaction found in different cases of the disease.

Finally, it may be pointed out that there is no histological evidence of neuronal storage in this condition. While it is known that in infantile Gaucher's disease nerve cells may degenerate and disappear without having previously stored lipid, there is little to suggest that this process occurs in Krabbe's disease. The degeneration of the dentate nucleus and inferior olive which has also been found in some other cases of the disease could be attributed to severe axonal damage. Similarly, the diffuse cerebellar atrophy in Case 3 might also have been secondarily introduced, since it was not sufficiently marked to invite comparison with the almost complete degeneration of the granular layer sometimes seen in amaurotic idiocy and metachromatic leucoencephalopathy. Striatal lesions were noted in our cases, as in that of Collier and Greenfield (1924), but it would be difficult to rule out the effects of anoxia

in their causation. In view of these non-specific neuronal changes and in the absence of visceral storage it does not seem justifiable to class Krabbe's disease as a lipidosis. Nor has chemical analysis shown a consistent increase in cerebroside over normal. The condition remains primarily a disease of myelinated axons.

Summary

The histological and chemical features of Krabbe's disease (globoid cell leucodystrophy) have been studied in three children, two of whom were siblings. Chemical analysis of the degenerated cerebral white matter in all three cases showed that neutral cerebroside was present in approximately normal amount, though there was a reduction in most of the other myelin lipids. In one brain which had been analysed before fixation in formalin the white matter contained substantially increased amounts of all the hexosamines and of neuraminic acid.

Histological examination in all cases demonstrated the characteristic globoid and epithelioid cell packets around vessels of precapillary size. In two cases the adventitial coat of the larger vessels in the white matter was thickened and contained spindle-shaped cells filled with granules staining more intensely with the periodic-acid-Schiff method than the globoid cells. It is considered that both types of cell are derived from the vascular adventitia, that they arise as a response to the presence of cerebroside in the tissues, and that there may be an associated abnormality in the adventitial cells themselves to account for this storage of lipid.

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INFANTILE METACHROMATIC LEUCODYSTROPHY

BY

J. W. BLACK and J. N. CUMINGS

From the Department of Pathology, University of Edinburgh, and the Department of Chemical Pathology, Institute of Neurology, the National Hospital, Queen Square, London

Metachromatic leucodystrophy is an uncommon type of diffuse cerebral sclerosis. This condition is found at various ages, but it is convenient to classify cases into congenital, infantile, juvenile, and adult varieties. The infantile form, which presents a fairly constant clinical and pathological pattern, was first described by Greenfield (1933) who recorded two cases; and four further examples were reported by Russell Brain and Greenfield (1950). Jervis (1960) found 10 cases in the literature with pathological observations and described two more. To these should be added one recorded by Jacobi (1947) in which metachromasia was subsequently demonstrated by Diezel (1957), and another briefly reported by Peiffer and Hirsch (1955). Other cases have recently been described by Norman, Urich, and Tingey (1960) and by Hagberg, Sourander, Svennerholm, and Voss (1960). This report describes the pathological and biochemical observations made in a further case.

Case Report

Clinical History.—The patient, a first child, was a full-term female born normally, after an uneventful pregnancy, to healthy parents. She developed normally and walked at 13 months. There were no illnesses of note until, at the age of 22 months, a tendency to stumble and fall appeared insidiously. This became progressively worse, clumsiness of upper limb movements developed, and she became incontinent. No convulsions were observed at this stage and there was no complaint of headache. When first seen in hospital at the age of 28 months, her gait was markedly ataxic, the limb muscles being hypertonic with exaggerated tendon reflexes, bilateral knee clonus and bilateral extensor plantar responses. In addition, there was incoordination of upper limb movements and fine horizontal nystagmus, but sensation appeared to be normal. Her speech was dysarthric and dysphonic with very slow articulation. Frequent extensor spasms were observed. There was no evidence of raised intracranial pressure and the fundi appeared normal. Physical examination was otherwise negative. The protein content of the cerebrospinal fluid was slightly elevated on two occasions at 60 mg. per 100 ml. and 50 mg. per 100 ml., but the cell count was not raised. The Wassermann reaction was negative and the Lange curve normal. As the patient's aunt suffered from hepatolenticular degeneration, investigations of copper metabolism were undertaken and this diagnosis excluded. Other biochemical and bacteriological investigations were negative, radiological examinations were not helpful, and two electro-encephalograms were reported as showing no significant abnormalities.

The diagnosis was thought to be diffuse sclerosis and no treatment was undertaken. Within two months the child was unable to walk, while a month later she could sit only with support. Her speech became more indistinct with a contracted vocabulary. Finally, she became unconscious in a state of decerebrate rigidity with numerous, severe convulsions which required continuous sedation with phenobarbitone. She died at the age of 34 months, the illness having lasted for one year. A sibling was alive and well at the age of 15 months.

Post-mortem Examination.—This was carried out by Dr. A. D. Bain within 12 hours of death. The body was that of a wasted female child showing no other external abnormalities. The gall bladder wall was moderately thickened and its lumen was filled by a pale grey papilloma. There was moderate tracheo-bronchitis but no pneumonia and the remaining viscera showed no macroscopic abnormalities. The skull, dura mater, and venous sinuses were normal. The brain, which weighed 1,000 g., and spinal cord were examined after fixation in 10% formalin. Apart from slight congestion of the cerebral leptomeninges, no external abnormality was noted. On section the cortical grey matter showed no unusual features. The white matter of the cerebrum, brain-stem, and cerebellum was firmer than usual and had a bleached appearance. Pallor of the thalami was seen and there was slight dilatation of the third ventricle. The spinal cord was firmer than usual but was of normal appearance externally and on section.

Histology of the Nervous System.—Paraffin-embedded and frozen sections were examined by various staining methods.

Cerebral White Matter.—There is almost complete demyelination in the corpus callosum, centrum semiovale, and convolutional white matter without sparing of the arcuate fibres, the optic tracts and radiations being less

severely affected. Surviving myelin sheaths are swollen, beaded, and fragmented. A reduction in the number of axis cylinders is evident, some interrupted fibres showing end bulbs. Loss of oligodendroglia is seen, paralleling the severity of demyelination. A moderate rod cell reaction is present but there are few neutral fat-containing foam cells and these are confined almost entirely to perivascular spaces. Fairly marked astrocytic proliferation is present throughout, binucleate and *gemästete* forms being seen, with dense, diffuse, fine, fibrillary gliosis (Fig. 1). Much metachromatic material is found in the demyelinated areas, largely within distended histiocytes. Smaller masses are seen lying free between glial fibrils, and some *gemästete* astrocytes contain, or show, surface encrustation by the same material (Fig. 2).

Cerebral Cortex.—The architecture is well preserved and most neurones appear normal, but in the deepest layers of the cortex a few are slightly swollen and contain intracytoplasmic metachromatic granules, usually with peripheral displacement of the nucleus. A few others show apparent encrustation of their surface and small aggregates of metachromatic material are seen lying free. Microglial and astrocytic proliferation accompany these changes.

Basal Ganglia.—Essentially similar changes are present here and metachromatic material is seen not only in the main white matter tracts but also, to a lesser extent throughout the grey matter masses in relation to traversing fibres. There is relative sparing of the ansa lenticularis (Fig. 3). Diffuse gliosis is present, particularly in the thalamus and a few neurones contain metachromatic material.

Brain-stem.—Severe demyelination is seen in the bases pedunculi and pyramids, the histological features being identical with those already described in the cerebral white matter. The spinocerebellar tracts are spared to a great extent; the superior, middle, and inferior cerebellar peduncles; the medial lemnisci; the medial longitudinal fasciculi; the tectospinal tracts, and the fibres emerging from the hilum of each inferior olive (Fig. 4). Oligodendroglial nuclei are seen in these tracts, though possibly in slightly reduced numbers. Many examples of neurones with intracytoplasmic metachromatic granules are found in the brain-stem, particularly in cranial nerve nuclei in the medulla but also, to a lesser extent, in the inferior olives and pontine nuclei.

Cerebellum.—The white matter shows similar features to that of the cerebrum. There is a possible slight deficiency of the granular cell layer. Patchy loss of Purkinje cells is evident, associated with proliferation of Bergmann astrocytes and isomorphous, fibrillary gliosis in the molecular layer. Little metachromatic material is present in the granular layer and none is seen in Purkinje cells or in the molecular layer. In contrast, all the neurones of the dentate nucleus contain many metachromatic granules and rod cell proliferation with gliosis is present here (Fig. 5).

Spinal Cord.—There is partial demyelination of the lateral and, to a lesser extent, anterior columns accompanied by fibrillary gliosis (Fig. 6). Many oligodendroglial nuclei persist in the affected tracts and only occasional metachromatic granules are seen. Some neurones of both the anterior and posterior horns contain the material and it is present also in partially demyelinated anterior nerve roots.

Cranial Nerves.—The olfactory tracts are only slightly involved. Myelination is well preserved in the optic nerves, but on passing backwards through the chiasma the fibres show progressively increasing damage. Other cranial nerves examined are patchily demyelinated and contain metachromatic material.

Throughout the central nervous system the leptomeninges and vessels are normal.

Peripheral Nerves.—No intact nerves were available for examination, but small granules of metachromatic material are seen in autonomic nerves in a heart section.

Staining and Other Properties of the Granular Material.—Frozen sections were stained with thionin or toluidine blue, according to the methods described by Leslie (1952), passed rapidly through graded alcohols and mounted in mersol. These preparations faded rapidly and more permanent results were obtained with cresyl violet using the method employed by Hirsch and Peiffer (1957). With thionin, the granules stain a reddish-brown colour initially, but dehydration results in a change, first to a dull olive green and then to a brilliant emerald green. With toluidine blue the material exhibits purple metachromasia, while the cresyl violet a rich golden-brown colour is obtained. No metachromasia can be demonstrated in paraffin sections.

Lipid.—The granular material stains very faintly orange with Scharlach R in frozen sections. Sudan black B stains it brown in paraffin sections and dark brown in frozen sections. Nile blue sulphate results in blue staining of the material in frozen sections.

Effect of Lipid Solvents.—Frozen sections, after being taken rapidly through the alcohols were left for 18 hours at room temperature in a variety of common solvents. They were then taken down to water and stained by the cresyl violet method. Metachromasia is completely lost after exposure to chloroform or pyridine, while xylol or benzene result in considerable diminution. Seventy-five per cent or absolute alcohol, acetone, or ether produce moderate loss.

Carbohydrates.—The periodic-acid-Schiff (P.A.S.) method stains the granules reddish-purple, more intense in frozen than paraffin sections. The material stains pink with Southgate's mucicarmine in both frozen and paraffin sections, and positively with alcian green.

Optical Activity.—In frozen sections only, some of the granules are birefringent.

Other Staining Reactions.—With Heidenhain's azan some of the granules stain blue and others are red, both being seen within the same aggregate or neurone. Blue-staining granules predominate in paraffin sections, red in frozen material. Similar, but sharper, differential staining is obtained using Lendrum's acid picro-Mallory method. The granules are eosinophilic and phloxinophilic; they stain dark blue with Mallory's phosphotungstic acid haematoxylin, dark grey with myelin stains and Hortega's method for axis cylinders, and pink with Cajal's gold sublimate.

FIG. 1.—Cerebral white matter. Astrocytic proliferation. Cajal × 135.

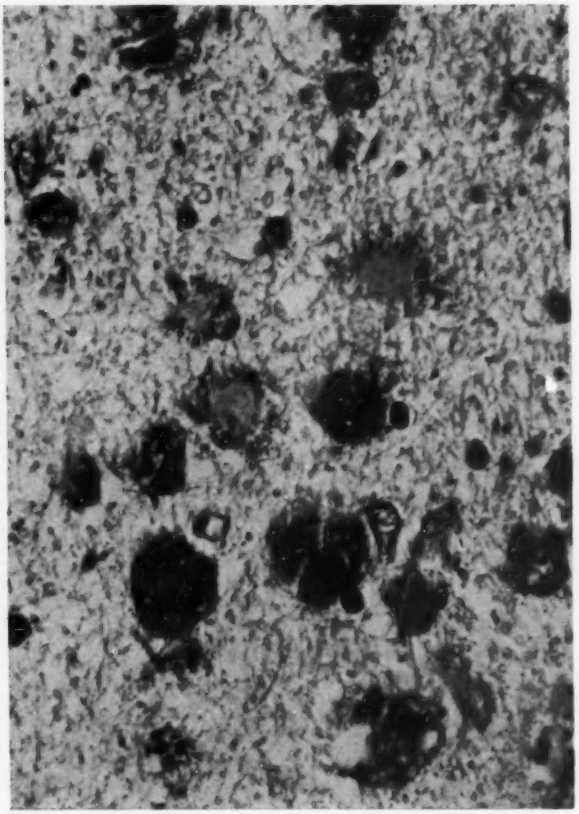

FIG. 2.—Cerebral white matter. Granular material within histiocytes and encrusting *gemästete* astrocytes. P.A.S. × 700.

FIG. 3.—Basal ganglion showing demyelination with relative sparing of the optic tract and ansa lenticularis. Loyez × 2.

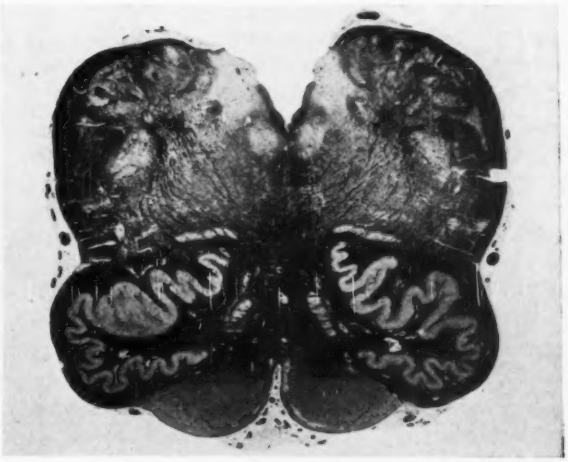

FIG. 4.—Medulla. Note preservation of many tracts and demyelination of pyramids. Loyez × 3.

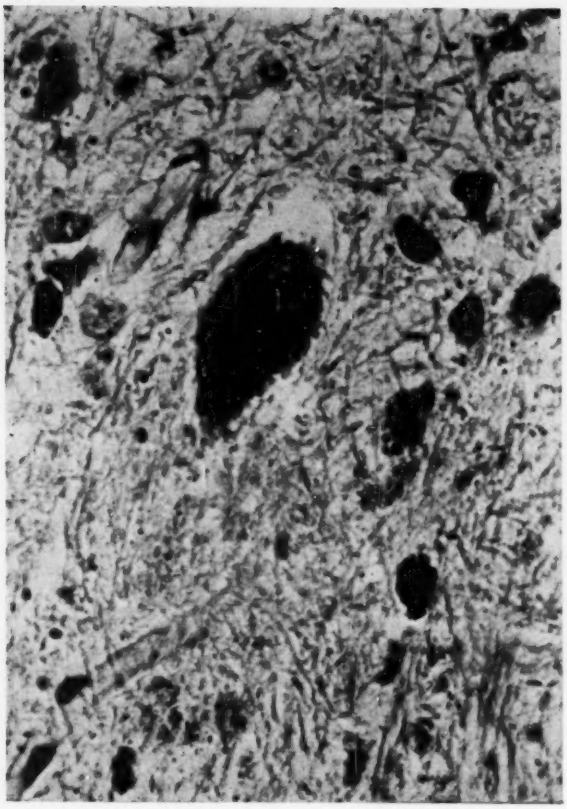

FIG. 5.—Dentate nucleus. Neurone distended with granular material. P.A.S. × 700.

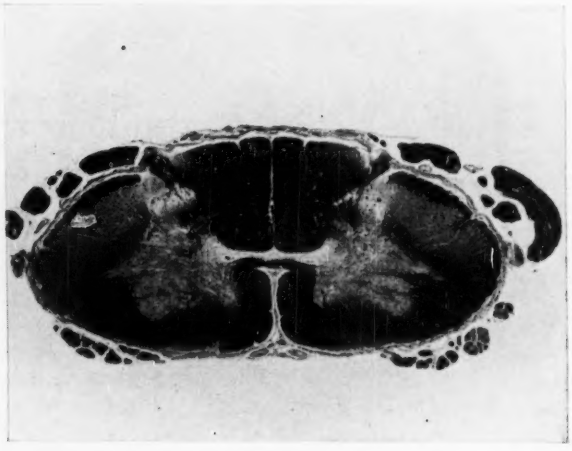

FIG. 6.—Spinal cord. Demyelination of lateral columns. Loyez × 3½.

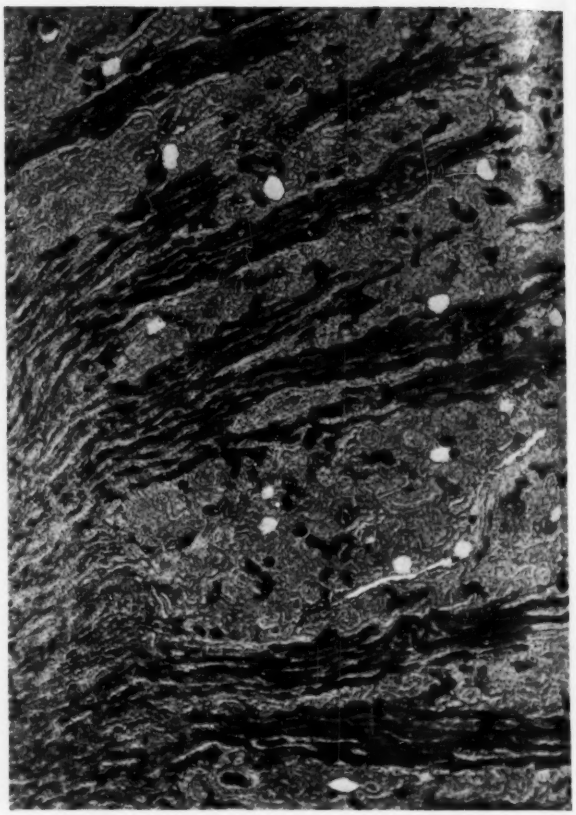

FIG. 7—Kidney: Metachromatic material in tubules. Cresyl violet × 30.

Histology of the Viscera.—In frozen sections of the kidneys large quantities of metachromatic material are seen in the slightly swollen epithelial cells of convoluted tubules (probably the distal), both limbs of Henle's loop and in collecting tubules (Fig. 7). Smaller amounts are present within the lumen of tubules but the glomeruli are normal. The affected cells stain poorly with eosin or P.A.S. in paraffin sections. The gall bladder papilloma is composed of a highly branched, vascular, connective tissue stroma covered by columnar epithelial cells which contain large amounts of metachromatic material. This is also present within histiocytes in the connective tissue stroma. Small quantities of similar material are seen in histiocytes in the portal tracts of the liver. Other organs examined contain no metachromatic material and are normal, apart from the lungs which show the usual feature of acute bronchitis and bronchiolitis.

Biochemical Studies.—Representative portions of the formalin-fixed brain and kidney were examined for various lipids, utilizing for their extraction the procedure of Folch, Lees, and Sloane-Stanley (1957a) using a 2:1 chloroform-methanol solvent (v/v). Water content, total phospholipid, total and free cholesterol were determined

as in previous examinations (Cumings, 1953). Hexosamine and neuraminic acid (gangliosides) were estimated (Cumings, 1957) as well as neutral cerebrosides (Radin, Lavin, and Brown, 1955). Cerebron sulphuric acid was estimated as barium sulphatides by the method of Radin, Martin, and Brown (1957), using the formula of Folch *et al.* (1957b). The galactose fraction of the barium sulphatide can be estimated by a suitable anthrone procedure and this has also been done and has given similar or identical results to the gravimetric procedure. The hexosamine fractions—lipid-soluble, water-soluble, and residual—have also been determined by methods similar to those of a previous report (Cumings, Goodwin, and Curzon, 1959). The results of these examinations can be seen in Table I.

TABLE I
CEREBRAL LIPIDS IN THE BRAIN

Substance	Cerebral White Matter		Cerebral Cortex	
	Patient	Normal	Patient	Normal
Total phospholipid	10·71	20·1	11·5	15·7
Total cholesterol	9·43	13·1	7·43	6·6
Esterified cholesterol	0·08	0·4	2·01	0
Neutral cerebrosides	6·36	7·14	—	—
Ganglioside	—	—	0·62	1·6
Lipid-soluble hexosamine	0·05	0·04	0·83	0·69
Water-soluble hexosamine	0·05	0·02		
Residual hexosamine	0·54	0·35		
Sulphatide	2·7	1·9	—	—
Water (%)	78·9	75·7	83·6	84·7

Results in g./100 g. dry tissue.

There is seen to be a well-marked loss of total phospholipid and of total cholesterol in the white matter with a slight loss of phospholipid in the cortex. Esterified cholesterol is present to an amount greater than the normal in the cortex but not in the white matter. Neutral cerebrosides in the white matter and gangliosides in the cortex are both reduced in amount. Total hexosamine in the cerebral white matter is increased, and this increase is due to a greater amount of residual hexosamine, for both the lipid-soluble and the water-soluble hexosamine fractions are within normal limits. These findings are similar to those previously described in post-mortem material (Cumings, 1957, 1960a, 1961). There is also a greater amount of sulphatide in the white matter than is present normally even though the tissue had been fixed in formalin for some months, and this is similar to the findings on other cases already reported at the London Conference on the Scientific Study of Mental Retardation in 1960 (see Cumings, 1961).

The sulphatide content in the kidney was 0·4 g. per 100 g. dry tissue and this is not raised to any appreciable extent as compared with the figures quoted by Austin (1960) for his normal controls, but at present there are no figures available for such controls using the method employed here.

Discussion

The clinical features observed in this case are very similar to those of other recorded examples except for the cerebrospinal fluid protein content, which in almost all has exceeded 100 mg. per 100 ml. Jefferson (1958) reported electro-encephalographic changes which he thought might prove of diagnostic value but these were not confirmed by Jervis (1960) nor in the present case.

Pathologically, all cases show diffuse demyelination, complete in some while in others, including this example, there has been comparative sparing of certain tracts. In general, as Russell Brain and Greenfield (1950) pointed out, the preserved pathways tend to be those which are myelinated at or shortly after birth. Neutral lipid is almost entirely absent and the striking feature is the presence of metachromatic material either lying free or within proliferated glial cells. In the literature, there is controversy as to whether microglia or astrocytes are involved, but in this case, as in those of Jervis (1960), both are implicated. The behaviour of the oligodendroglia is variable. Russell Brain and Greenfield (1950) emphasized their disappearance or considerable reduction not only in demyelinated areas, but also in well-preserved tracts, and they considered this to be evidence for a primary disorder of oligodendroglia. Similar observations have been made in some recorded cases while in others, including the present one, oligodendroglial loss has parallelled the severity of demyelination. Jervis (1960) found that they were irregularly involved and saw many areas with no evident decrease. Lumsden (1951) suggested that an enzymatic abnormality of the oligodendroglia resulted in abnormal myelin metabolism and accumulation of the metachromatic lipid which normally appears briefly as a catabolic product. Diezel (1957) agreed with this view, without specifically implicating the oligodendroglia. On the other hand, Feigin (1954) described the case of an infant dying a few weeks after a premature delivery and pointed out that as very little myelin could have been present at birth, the metachromatic material was unlikely to have been derived from its breakdown.

In almost all reported cases metachromatic material has been observed within the cytoplasm of neurones, particularly in the dentate and brain-stem nuclei. The affected cells are distended and the nucleus is displaced peripherally, producing a resemblance to the neurones seen in amaurotic family idiocy and other cerebral lipidoses. This observation led Norman (1947) to the conclusion that metachromatic leucodystrophy should be regarded as closely related to the lipid storage disorders and he commented that demyelination occurs in these, while in no other demyelinating condition are catabolic products found in neurones. His views, later endorsed by Hirsch and Peiffer (1957), by Edgar (1957), and by others, represent the current opinion on the nature of the disease.

Metachromatic material in other organs, particularly the kidneys, liver, and gall bladder, where papilloma formation has been described (Norman, 1947), has been noted in several cases, but it remains uncertain whether this is evidence of a generalized disorder or merely an indication of excretion of the material. Certainly the visceral deposits in the present case, as Russell Brain and Greenfield (1950) also found, do not appear to be histochemically identical with those in the nervous system.

Extensive histochemical studies of the metachromatic material in cases from various age groups have been carried out by Diezel (1957) and by Hirsch and Peiffer (1957) in addition to observations reported in individual examples. Even allowing for technical variations, conflicting results have been obtained (Feigin, 1954). Thus, the material stained positively with techniques for mucin and related substances in our case and in those of Russell Brain and Greenfield (1950) and of Hain and LaVeck (1958), whereas Leslie (1952), Norman *et al.* (1960) and Jervis (1960) reported it to be negative. Furthermore, although metachromasia is lost in paraffin-embedded tissue, positive staining with P.A.S. is retained, pointing to at least two compounds being present. This view is reinforced by the ability to obtain differential staining of the granules, a feature also found by Russell Brain and Greenfield (1950), by Leslie (1952), and by Bertrand, Thieffry, and Bargeton (1954). Certain properties are common to most cases. The material is acid, P.A.S. positive, and stains with Sudan black B and Nile blue sulphate but only faintly with Scharlach R. There is general agreement that it is a glycolipid, and Diezel (1957) showed that it was not identical histochemically with the cerebrosides of the myelin sheath nor with the ganglioside found in distended ganglion cells in amaurotic family idiocy. The metachromatic material is almost certainly the sulphatide demonstrated chemically.

In 1957, Edgar examined formalin-fixed material from 11 cases of metachromatic leucodystrophy and found levels of lipid hexosamine raised above the normal. Cumings (1957, 1959) also reported on cases verified histologically which showed a raised level of total hexosamine. Blackwood and Cumings (1959) have recorded seven cases of this disease diagnosed biochemically from the raised level of total hexosamine in cerebral biopsy material and four of them were verified histologically. There are four other cases recorded, two by Cumings (1960a) and two by Tingey (1959), in all of which raised levels of total hexosamine were found. All these cases were confirmed by histological examination of necropsy material.

One of us (Cumings, 1961) has examined seven cases confirmed by necropsy and in all increased amounts of total hexosamine were found in the cerebral white matter, and in three out of four of these cases in which the examination has been performed increased sulphatides have been found.

Jatzkewitz (1958, 1960) obtained some evidence of a raised content of sulphatide in the brain, more especially when it was calculated against the sphingolipid fraction of the cerebral lipids, but his technique was different from that used here. Austin (1957) drew attention to the presence of metachromatic material in the urine and in 1960 he further showed that there was an increase in the amount of cerebroside sulphuric acid esters in the cerebral white matter and in the kidney. One of us (J.N.C.) has found metachromatic material in the urine (Cumings, 1960b) from such patients but has also found it to be present in non-catheter specimens from young female children. The amounts of sulphatide found by Austin (1960) in normal white matter are very similar to those found by us as well as by Hagberg *et al.* (1960) who described two cases of metachromatic leucodystrophy with raised levels sulphatide. The results of Jervis (1960) for sulphatides in his two cases are very similar to those of Austin, Hagberg *et al.*, and ourselves. Norman *et al.* (1960) have recently described two further cases and Mossakowski, Mathieson, and Cumings (1961) have recorded three cases in one family.

The diagnosis can be made with a considerable degree of certainty from the findings of raised levels of total hexosamine and of sulphatides in either biopsy material or in the brains of cases examined at necropsy.

Summary

The clinical, pathological, and chemical findings in a case of infantile metachromatic leucodystrophy are described.

Metachromatic granular material had accumulated in areas of demyelination, within certain neurones, and in the kidney, liver, and in a papilloma of the gall bladder. Increased quantities of total hexosamine and sulphatide were present in the cerebral white matter, confirming the findings in other reported cases.

The relationship of metachromatic leucodystrophy to the cerebral lipidoses is discussed.

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THE EFFECTS OF HEMISPHERECTOMY ON INTELLECTUAL FUNCTIONING IN CASES OF INFANTILE HEMIPLEGIA

BY

JOHN McFIE

From the National Hospital, Queen Square, London

The recent increase in the number of reports of results of hemispherectomy, after which the majority of patients show considerable clinical improvement, prompts an inquiry into the effects of this operation on the exercise of intellectual abilities, and their implications for the understanding of cerebral organization.

Until a decade ago, the operation was rarely performed, and then usually for the removal of extensively infiltrating gliomata. Moreover, the majority of these removals were of the right hemisphere: of 16 cases collected by Mensh, Schwartz, Matarazzo, and Matarazzo (1952), only one, that of Zollinger (1935), was of a left hemisphere. Hillier (1954) reported another case of left hemispherectomy for glioma, and in the series of Gardner, Karnosh, McClure, and Gardner (1955) there was one case of left-sided removal. Earlier accounts (Dandy, 1928; Gardner, 1932; Diven, 1934; Rowe, 1937) did not report any psychological impairment following the right-sided operation; however, the patients were not given performance tests of the kind sensitive to right hemisphere lesions, and the more detailed studies of Gardner *et al.* (loc. cit.) led these authors to conclude that 'removal of a cerebral hemisphere left the patients with defects in judgment and inability to plan for the future; and in all patients psychometric studies indicated an impairment in insight, in emotional control, in initiative, and in perseverance'. In the three cases of left hemispherectomy (Zollinger; Hillier; Gardner *et al.*) speech disturbance was associated with a marked degree of intellectual impairment, but the dissolution of language was not absolute and in the youngest patient (that of Hillier, a 14-year-old boy) a considerable improvement in speech was observed during the two years following operation. In general, then, the psychological results of hemispherectomy for glioma are seen to be, when the left hemisphere is involved, a profound but not absolute impairment of speech, and when the right hemisphere is involved, at least a reduction in judgment and insight.

In cases of infantile hemiplegia, on the other hand, the changes reported are entirely different. Williams and Scott (1939) gave a brief description of a patient aged 20 years, who had suffered a left cerebral injury at the age of 3 weeks: removal of the damaged hemisphere resulted in 'no apparent mental deterioration', and two years later the patient was able to cooperate intelligently as a subject in a physiological experiment. One of the four patients of Marshall and Walker (1950) was a case of birth injury to the right hemisphere; and it is interesting to note that in this patient speech was reported to be more retarded in development than was walking. It was Krynauw (1950), however, who suggested the operation as a therapeutic measure, and presented a series of 11 patients with infantile hemiplegia and epilepsy, ranging in age from 7 months to 21 years, who had improved after hemispherectomy. In one (Case 10) partial ablation resulted in no improvement, and the entire hemisphere was removed at a second operation. In 10 of the patients, it was the left hemisphere which was involved; yet in none of these was any significant impairment of speech reported as a consequence of the operation, and in some there was striking improvement. In all except one of these patients, the injury was in the first 10 months after birth; in the remaining one (Case 9) there was a history both of difficult birth and of a severe febrile illness at 4½ years. From this evidence, Krynauw argued not only that removal resulted in liberation of the remaining hemisphere from the 'abnormal influences of the pathological side', but also that 'with regard to language function . . . hemisphere dominance had adjusted itself before the removal of the affected hemisphere, and that it was the minor hemisphere which was removed in all cases'. Krynauw did not make any statement about the age at which this 'adjustment' might take place: Obrador (1951), however, reported four cases of hemispherectomy, one of which (Case 3) was of the left hemisphere in a child of 7 years, who had been normal and right-handed until the age of 5, when a

meningitic infection had left her with a right hemiplegia and dysphasia. Removal of the left hemisphere resulted in no increase in the dysphasia but in an improvement in speech. Obrador concluded that 'up to the age of 5 years language functions can be integrated in the right hemisphere'.

Cairns and Davidson (1951) presented the results of hemispherectomy on three patients to a meeting of the Neurological Section of the Royal Society of Medicine. In addition to clinical improvement, every patient showed an increase in score on psychological tests after the operation, the average being in the region of 20 points of I.Q. Two of the operations were on the right side and one on the left, but only in Case 2 (right-sided, for Sturge-Weber-Dimitri disease) can the age of injury be inferred from the reports. At the same meeting, McKissock and his colleagues (unpublished) reported a series of 11 hemispherectomies, seven right and four left, and I observed that in only one patient (whose left hemisphere was injured at 20 months) had there been a fall in I.Q. after operation, but that in the majority of patients language abilities were inferior to abilities on performance tests, irrespective of which hemisphere was damaged. With the younger children and defectives, this amounted to virtual absence of language, while motor performances were at a considerably higher level; on the Terman-Merrill scale, some reached a higher standard on the non-verbal than on the verbal items, and on the Bellevue scale, this discrepancy was represented in the difference between I.Q.s on the verbal and performance parts of the test. McKissock (1953) reviewed his experience of 18 hemispherectomies, and established firmly his criteria for recommending the operation, namely, the coexistence of infantile hemiplegia with epilepsy and behaviour disorder.

Achslogh and Ectors (1954) reviewed the literature of hemispherectomies to that date, which, they stated, 'must exceed a hundred'. Their own patient was aged 17 years, with a right hemiplegia following a febrile illness at the age of 9 months. Before the operation the patient refused to do any tests, but after left hemispherectomy (the authors observe that it should really be called hemidecortication) his Terman-Merrill I.Q. was 87, with an almost 'average adult' vocabulary. The authors noted that 62% of the hemispherectomies published were of the left side, yet in no case of infantile hemiplegia had this resulted in aphasia. Perlstein and Sugar (1954) reported briefly on two hemispherectomies, one right and one left, for infantile hemiplegia; Sugar stated 'in communication with Dr. J. M. Nielsen, I learned that if the speech center is damaged before the age of 10, the child will recover his speech'. Uecker, French, and Johnson (1954) reported the results of psychological tests of hemispherectomy in seven epileptic hemiparetics, injured 'in infancy or early childhood'. They took particular care to eliminate practice effects by using different forms of tests on each occasion or by delaying retesting with identical tests: the results showed no marked losses following operation, and some improvement in the two patients whose pre-operative I.Q.s were near the average normal level. Unfortunately, in no case was the side of operation or actual age of injury stated. Zülch (1954) described two cases: the first, aged 27, with birth injury of the left hemisphere, began to walk at 13 months and first spoke at 3 years, and had 'an average intelligence, which was not changed' after hemispherectomy. The second, aged 5, with a birth injury to the right hemisphere, had an intelligence 'in keeping with her age', and was improved following operation.

In addition to their cases of hemispherectomy for glioma, Gardner *et al.* (1955) described a 29-year-old infantile hemiplegic, with a verbal I.Q. of 67 which rose, 37 days after right hemispherectomy, to 78. Comparison with the other patients showed that hemispherectomy for glioma resulted in more impairment than for infantile hemiplegia, and the authors concluded that 'immature cortex can acquire functions planned for the cortex of the other side, but (with the possible exception of speech) once a function has become established in the cortex it cannot be transferred'. 'Transfer' is perhaps not the best definition for acquisition of a function by an area of cortex following excision of the area previously exercising that function; and, as far as psychological abilities are concerned, there is no direct evidence of the exercise of any other function than that of speech. None of the reports is concerned with arithmetical ability, visual-spatial analysis, or any other specific ability, and even reading and writing are only briefly mentioned in a few cases.

In fact, the criticism of Mensh *et al.* (1952) that earlier reports were mostly 'in general terms' rather than detailed accounts may be levelled also at subsequent studies. In very few cases are the side damaged, the age at injury, and the pre- and post-operative scores (or changes) on tests, given for each patient. Nevertheless, certain definite conclusions may be drawn from the foregoing series, and certain questions asked. Perhaps the clearest inference, following upon the descriptions of cases of early injury to the left hemisphere without marked disturbance of speech, is that, as Krynauw put it, 'hemisphere dominance had adjusted itself before removal of the affected hemisphere'. This immediately raises two questions: Is there a critical age beyond which this adjustment does not take place? And is there a similar adjustment in respect of 'right hemisphere

functions', such as spatial analysis, in cases of damage to the right hemisphere? A third, subsidiary question might be asked: Is there similar adjustment, in cases of left hemisphere injury, of other 'left hemisphere functions' such as calculation, abstraction, and constructional ability (c.f. McFie and Piercy, 1952)? The answer to the question of age of adjustment may be that it is a gradual process. In none of the patients with birth injury was any reduction in speech reported after the operation; in Krynauw's Case 3, injured at 10 months, speech was impaired immediately following (left) hemispherectomy, but later improved greatly; Obrador's Case 3 appears to have been normal up to 5 years, when the left hemisphere was injured with resultant dysphasia, and two years later hemispherectomy resulted in improvement in speech; according to Sugar, Nielsen asserted that recovery of speech would take place if the damage had been done before 10 years; and the case of Hillier makes it clear that considerable improvement is possible even after 14 years of age. Nevertheless, it appears to be possible to distinguish between the results of birth injury, in which no impairment of speech follows left hemispherectomy, and of injury at some later age, in which removal results in deficit but is followed by improvement. It may be of some theoretical interest, and of clinical value, to establish whether or not such a critical age exists. The question of adjustment of other functions, or of their establishment in the undamaged hemisphere, cannot be answered from the foregoing reports; in very few cases was any other psychological ability than speech studied in sufficient detail.

Another conclusion which is affirmed by several authors is that greater improvement in cases of infantile injury results from complete hemispherectomy (or hemidecortication) than from partial removal of a damaged area even if the remaining cortex appears normal. Laine, Fontan, Delandtsheer, and Delandtsheer (1951) compared the results of 14 cases of various types of restricted operation with two cases of hemispherectomy, and concluded 'we must abandon localised intervention in these cases: we must follow the Anglo-Saxon example of preference for hemispherectomy'. Krynauw suggested that the remaining hemisphere was able to function normally once it had been 'released from abnormal influences from the pathological side'. In view of the almost unaminous agreement on the beneficial effects of the operation, it is of interest to ask what is the extent of the improvement, whether it varies with side affected, and to what influences it may be attributed. Many of the patients reported were mentally defective, but even the most sceptical authors, Uecker *et al.*, reported the greatest post-operative improvement in those patients whose pre-operative I.Q.s were nearest to normality; therefore it may be that those with the highest pre-operative levels show the greatest benefits. Table I summarizes the post-operative I.Q.s of patients in the studies quoted. It will be noted that the mean I.Q. is 63·4, and that the distribution is skewed, with a preponderance of individuals with low values.

TABLE I

I.Q.s AFTER HEMISPHERECTOMY FOR INFANTILE HEMIPLEGIA IN PUBLISHED CASES

Authors	Case Number	I.Q.
Cairns and Davidson (1951)	1	111
	2	74
	3	106
Achslogh and Ectors (1954)	1	87
Uecker *et al* (1954)	1	37
	2	20
	3	18
	4	16
	5	76
	6	88
	7	38
Gardner *et al* (1955)	1	78
French *et al.* (1955)	1	82
		Mean 63·4

There remains my earlier suggestion that infantile hemiplegics show an impairment of language ability, irrespective of the hemisphere actually damaged, in comparison with their non-language functions. If confirmed, this would dispose of the earlier question concerning pre-operative 'adjustment' of right hemisphere functions; it would appear to be more efficient than that of left hemisphere functions. Again, however, the question of age would be raised. Is there evidence of a critical age at which this apparent relative impairment of language functions is replaced by the usual pattern of impairment according to hemisphere affected?

Present Study

The number of hemispherectomies for juvenile hemiplegia performed at the National Hospital is now over forty: the clinical indications and operative technique have already been made clear (McKissock, 1953, 1954). Of these patients, psychological test records are available for 34, and, in addition, records are available for nine patients who underwent partial removals, *i.e.*, excision of evidently damaged tissue. (One of these subsequently had the rest of the hemisphere removed, and is therefore in both groups.) The clinical indications for the two types of operation were essentially the same. The relevant information about the patients is given in Table II. The intelligence quotients are those achieved on whatever test was appropriate to the patient's level: for the

TABLE II
PARTICULARS OF PATIENTS

Patient No.	Hospital No.	Age at Injury	Hemisphere	Pre-operative I.Q.	Age at Operation (years)	Post-operative I.Q.	Post-operative E.E.G.	Pathology
A Hemispherectomy								
1	15623	Birth	R	29	5	35	N	Porencephalic cyst
2	20809	Birth	L	23	11	23	1	Diffuse changes
3	22069	Birth	R	(a)*	4	—	2	Porencephalic cyst
4	23239	5 yr.	R	64	10	60	3	Diffuse changes
5	22684	Birth	R	75	20	91	N	Porencephalic cyst
6	22797	15 mth.	R	48	7	43	2	Diffuse changes
7	25473	Birth	R	13	23	19	1	Porencephalic cyst
8	27415	3 mth.	L	55	21	62	N	Porencephalic cyst
9	29312	20 mth.	L	38	12	25	3	Diffuse changes
10	29310	6 mth.	R	37	13	38	1	Diffuse changes
11	616	Birth	R	35	14	40	2	Diffuse changes
12	29776	Birth	R	73	18	88	N	Porencephalic cyst
13	30185	15 mth.	L	67	5	67	N	Porencephalic cyst
14	31140	2½ yr.	R	(b)†	25	(b)	1	Diffuse changes
15	14805	Birth	L	79	23	93	N	Porencephalic cyst
16	34270	Birth	L	50	3	50	1	Diffuse changes
17	34357	Birth	R	47	19	55	1	Sturge-Weber-Dimitri disease
18	36382	3 mth.	L	(a)	6	—	3	Diffuse changes
19	38776	12 mth.	R	66	13	66	1	Diffuse changes
20	39712	3 mth.	L	43	5	83	2	Diffuse changes
21	36517	4 mth.	L	30	1	62	N	Porencephalic cyst
22	42162	Birth	R	75	7	65	N	Sturge-Weber-Dimitri disease
23	43346	3 yr.	R	27	12	38	1	Diffuse changes
24	51472	21 mth.	L	75	3	75	N	Diffuse changes
25	51025	Birth	L	48	13	66	N	Porencephalic cyst
26	52847	6 mth.	L	35	2	47	3	Diffuse changes
27	52665	Birth	R	53	19	65	1	Diffuse changes
28	55734	11 mth.	R	55	7	(c)‡	(c)	Diffuse changes
29	57057	Birth	R	51	7	59	2	Diffuse changes
30	57161	Birth	R	59	31	(c)	1	Diffuse changes
31	59160	Birth	L	69	15	74	N	Porencephalic cyst
32	61924	Birth	R	80	24	90	N	Porencephalic cyst
33	29350	Birth	R	68	11	(c)	(c)	Diffuse changes
34	50512	10 mth.	R	81	22	93	N	Diffuse changes
B Partial Removals								
1	12534	Birth	R	116	15	108		
2	16235	3 mth.	L	61	18	58		
3	13769	Birth	L	71	25	69		
4	616	Birth	R	40	13	36		
5	33202	2 yr.	R	74	4	71		
6	39232	Birth	L	70	11	77		
7	39401	6 mth.	R	72	9	59		
8	46620	Birth	R	69	15	66		
9	68285	Birth	R	100	12	102		

(a)* Too low to be scored.
(b)† Patient's English only fragmentary.
(c)‡ Not seen after operation.
E.E.G.: N, no abnormality in remaining hemisphere; 1, slight abnormality; 2, moderate abnormality; 3, gross abnormality.

grossly defective children, on Griffiths' developmental scale; for the intermediate groups, on the Terman-Merrill scale; and for the higher levels, on the Wechsler-Bellevue scale. The description of post-operative E.E.G.s is limited to the presence or absence of major abnormalities as reported at the time of recording, particularly of slow waves, of fast activity, or of foci of spike discharges. The description of pathology in the removed hemisphere is limited to three categories: porencephalic cyst; diffuse scarring and atrophy; and unilateral Sturge-Weber-Dimitri disease (cutaneous-leptomeningeal angiomatosis).

Intelligence Quotients.—The level of two children was so low as to be unscorable on any scale, one was of foreign birth and education, and three patients were not seen post-operatively. The scores of the remaining 28 patients at intervals after the operation are represented graphically in Fig. 1. The distribution of the pre- and post-operative intelligence quotients is shown in Table III. This includes the grossly defective patients, and also those seen on one occasion only. The scores were all on the same tests as those given pre-operatively, and there is therefore a possibility that some of the increases may be due to the effect of practice. While this may reduce the significance to be attributed to a number of increases, it must by the same token throw emphasis on those

TABLE III
DISTRIBUTION OF INTELLIGENCE QUOTIENTS

I.Q.	0-19	20-39	40-59	60-79	80-99
Number of patients pre-operative	3	8	10	10	2
Number of patients post-operative	3	5	6	10	6

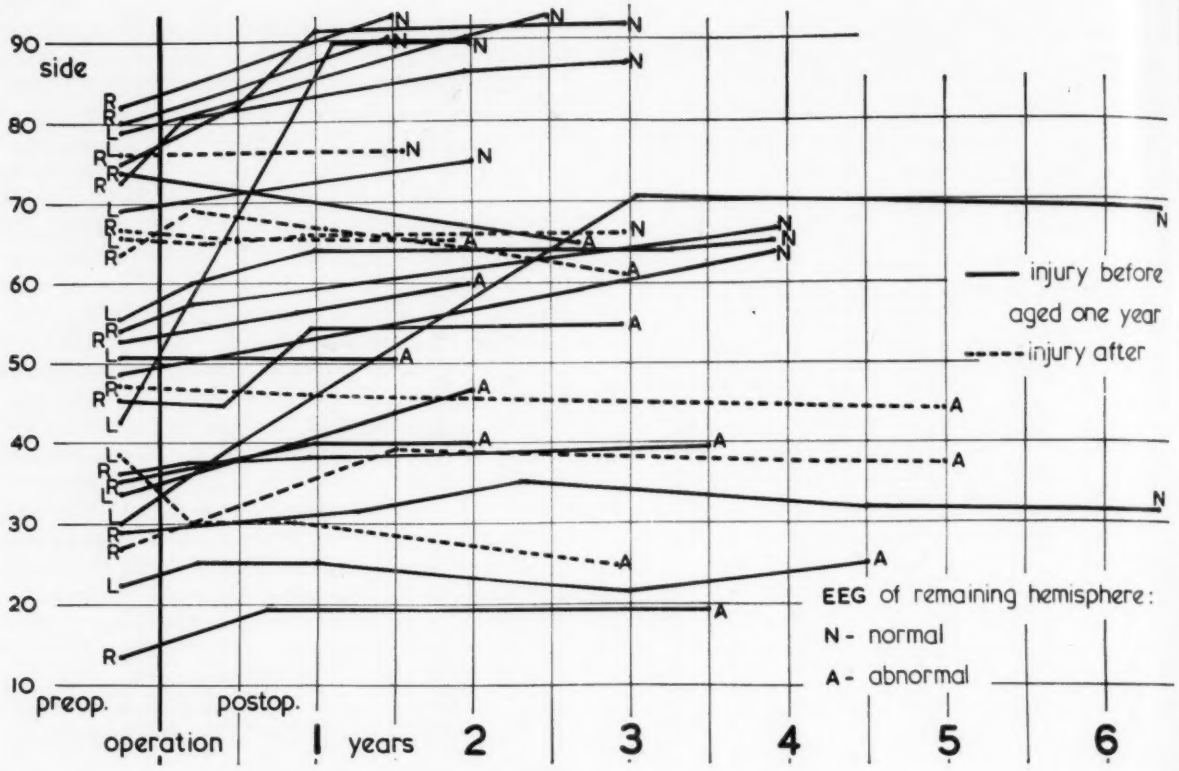

FIG. 1.—Changes in intellectual level after hemispherectomy.

cases in which increase is absent or in which there is a fall in score.

For the purpose of evaluating the changes in intelligence, the score at retesting at an interval nearest to two years after operation has been used, and the average change between the pre-operative score and this retest score is given, for various groups, in Table IV, together with the significance of the difference between groups. The mean change for the whole series of hemispherectomies is nearly + 8 points of I.Q., and this differs significantly from the average for partial removals, namely, 3 points. Between left and right hemispherectomies, on the other hand, the difference in change is not significant. This might have been the consequence of differences in pre-operative intelligence between the two groups, but again the slight difference is not significant.

Since it is likely that the remaining hemisphere was not entirely free of pre-operative pathology in all cases, the average change in I.Q. has been compared for groups with evidence of various degrees of abnormality in the post-operative E.E.G.s; apart from a fall in the group with the greatest abnormalities (three patients only), there is no evidence of associated differences. Between the group with porencephalic cysts in the removed hemisphere, and those with other changes, the difference in change in I.Q. does not reach the conventional level of significance, but may be regarded as worth further investigation.

Age of Injury.—The most striking difference in mean change, however, is that associated with the age at which the injury to the hemisphere occurred. The positive change in those injured at birth and in the first 12 months of life contrasts with the negative change in the group injured after 1 year of age. The alteration in I.Q. is shown in Fig. 2 to occur in association with injuries after 11 to 12 months of age, and the difference between averages for the birth-and-infantile groups, compared with the juvenile group, is highly significant. In the light of this evidence, it is necessary to re-examine the comparisons of Table IV, omitting the scores of the seven patients with juvenile injury, since these may have obscured differences in the infantile injury group. In the comparison of partial with total removals, this correction leaves the average for the group with partial removals the same, but increases the change in the group with total removals, thus further emphasizing the difference. With regard to hemisphere damaged, the correction results in a slight

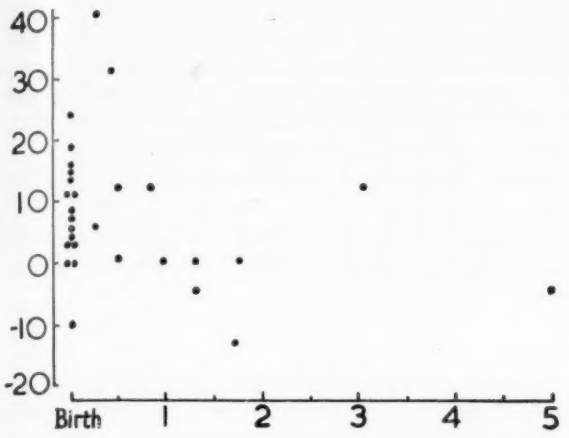

FIG. 2.—The relationship of change in I.Q. after hemispherectomy to age at which the hemisphere was injured.

increase of both averages, without increase in significance. In the E.E.G. groups, the correction has the effect of removing the two negative scores from the last group (3); the remaining patient showed a change of + 12 I.Q. points, and the variation between groups practically disappears. The suggestive difference between cyst and non-cyst groups also disappears after the correction, since none of the cases of juvenile injury is in the group with cysts. The general effect, then, of omission of these patients is to confirm the significant conclusions which may be drawn from the data in Table IV.

Other variables which may be associated with post-operative change in intellectual level are the age at which operation is undertaken, and the patient's pre-operative intellectual level. Correlation coefficients between these variables have been computed for the infantile injury group, *i.e.*, excluding those with injury over 1 year of age, and are (1) change in I.Q. with age at operation, $r = -0{\cdot}02$ (not significant); and (2) change in I.Q. with pre-operative I.Q., $r = 0{\cdot}07$ (not significant). There is thus no evidence of association between change in I.Q. and either of these variables. It is interesting to note that for the correlation (3) of age at operation with pre-operative I.Q., $r = 0{\cdot}362$. For 21 observations, this just exceeds the $P = 0{\cdot}1$ level of significance, and may be regarded as indicative of a reluctance on the part of the surgeon to operate on apparently intelligent young children.

Differential Impairment.—So far, the only measure of intellectual level which has been considered is the intelligence quotient. This has the advantage that it is a measure related to the normal levels of achievement at each age, which is provided by every test; and, while not strictly comparable between tests, may nevertheless be used to estimate changes on retesting with the same test. On the other hand, the I.Q. is unsatisfactory in that it is a measure of total achievement, and provides no information on the subject's relative levels in different fields of intellectual function. In making comparisons of the effects of lesions in each hemisphere, it is essential to obtain separate measures of different abilities, in particular of those in the verbal and non-verbal (or 'performance') fields. For these to be accurately compared, it is necessary to have scores on different subtests, and the only test of this type used in the present study was the Bellevue scale (Wechsler, 1944). However, in only six of the patients was the intellectual level sufficient to enable them to attempt this scale. The pre-operative subtest scores and verbal and performance I.Q.s of these patients, together with the post-operative changes, are given in Table V, and of other tests in Table Va. The numbers are too small for significant statistical comparisons to be made, but it will be seen that both

TABLE IV

MEAN CHANGE IN I.Q. APPROXIMATELY TWO YEARS AFTER OPERATION IN DIFFERENT CLINICAL CATEGORIES

1 Nature of Operation		
Total Hemispherectomy n = 28	Partial Removal n = 9	Significance of Difference
7·72	−3·00	P <0·01

2* Side of Hemispherectomy		
Left n = 11	Right n = 17	Significance of Difference
10·46 (51·0)	5·95 (54·8)	n.s. (n.s.)

3† E.E.G. of Remaining Hemisphere			
Normal n = 13	1 n = 8	2 n = 4	3 n = 3
9·31	6·33	12·00	−1·67

4 Nature of Pathology in Removed Hemisphere		
Porencephalic Cyst n = 10	Diffuse or Sturge-Weber-Dimitri n = 18	Significance of Difference
12·9	4·80	P < 0·1

5 Age at Time of Injury		
(a) Birth n = 15	0-11 months n = 6	Over 1 year n = 7
7·53	16·67	−1·57
(b) Under 1 year	Over 1 year	Significance of Difference
10·07	−1·57	P < 0·01

*The figures in brackets are mean pre-operative I.Q.s.
†The figures 1, 2, 3 represent different degrees of abnormality.

TABLE V

RESULTS ON WECHSLER-BELLEVUE TESTS

Case Number	Digit Span	Arithmetic	Similarities	Vocabulary	Verbal I.Q.	Picture Completion	Pictorial Arrangement	Block Design	Digit Symbol	Performance I.Q.
Left Hemisphere										
8	3 (+3)	0 (0)	2 (+1)	3 (+1)	57 (+7)	8 (+4)	4 (0)	7 (0)	3 (−)	61 (+8)
15	4 (+5)	7 (+2)	8 (+1)	7 (+2)	82 (+15)	8 (−)	8 (−1)	8 (+3)	5 (−)	80 (+9)
Right Hemisphere										
5	6 (0)	4 (0)	7 (1)	6 (0)	70 (+7)	11 (+1)	6 (+4)	9 (+2)	4 (+5)	85 (+24)
12	4 (0)	3 (0)	5 (+2)	5 (+1)	68 (+8)	14 (0)	8 (−1)	7 (+2)	4 (0)	85 (+7)
17	2 (−2)	0 (+1)	5 (+2)	4 (0)	58 (+1)	3 (−1)	3 (−2)	3 (0)	2 (0)	47 (−3)
34	4 (0)	10 (0)	7 (+1)	6 (+1)	80 (+7)	10 (0)	6 (+3)	9 (+1)	7 (+3)	85 (+16)

— = Test not done. ( ) = Change in score after operation.

TABLE Va

RESULTS ON ADDITIONAL TESTS

Case Number	Weigl's Sorting	Sentence Learning	Memory Design
8	F (P)	7 (0)	1 (+)
15	F (P)	— (—)	4 (0)
5	F (F)	9 (+1)	4 (0)
12	F (P)	9 (0)	4 (0)
17	F (F)	— (—)	— (—)
34	— (—)	10+ (−3)	4 (0)

— = Test not done
( ) = Change in score after operation.
Weigl's Sorting: F, failed; P, passed; ( ) post-operative result.
Sentence Learning: Score = number of repetitions required to learn.

with left- and right-sided lesions all patients but one scored higher on performance than on verbal tests, and that in general (again with the exception of one case) the post-operative increases were greater on performance than on verbal tests. These differences are emphasized by the results of the additional tests shown in Table Va. The failures on Weigl's test and on the sentence learning test (normally learnt in five repetitions), in contrast to the majority obtaining a maximum score (four points) on memory for designs test, is conventionally characteristic of left hemisphere lesions (McFie, 1960). Two points are noteworthy: that all these patients are in the group of infantile injuries, *i.e.*, under 1 year of age, and that the case with anomalous results (Case 17) was one of Sturge-Weber-Dimitri disease.

Whether there is a similar discrepancy between verbal and performance level in the remaining patients cannot, as has been explained, be assessed as accurately as in those able to attempt the Bellevue scale. It is possible, however, to make a rough estimate of the relative levels reached, by comparison of the age levels reached in verbal and performance parts of Griffiths' developmental scale, and by examination of the individual items passed in the Terman-Merrill scale. Moreover, since this comparison concerns only pre-operative scores, it is possible to include in the classification the patients who ultimately underwent only partial removal. Table VI shows the number of patients with left- and right-sided lesions, subdivided according to the relative impairment of their abilities, *i.e.*, whether their general verbal level was lower than their performance level, or *vice versa*. With conventional cerebral organization, it would be expected that a greater number with left-sided lesions would show verbal deficits, and a greater number with right-sided lesions, performance deficits. In fact, the data in Table VI show that there is a large group of patients

TABLE VI

RELATIVE IMPAIRMENT IN WHOLE SERIES

		Side of Lesion	
		Left	Right
Relative loss	Verbal	9	15
	Performance	4	8

with apparently anomalous verbal deficit in association with right-sided lesions. We have seen (Table V) that this association occurred in a small group of patients with infantile, *i.e.*, at birth or under 12 months, injury: it is therefore relevant to inquire whether this association is significant for the series as a whole, and whether it varies with side of lesion. Table VII shows that relative verbal impairment is

TABLE VII

RELATIVE IMPAIRMENT ACCORDING TO SIDE AND AGE OF INJURY

Side of Lesion		Left		Right	
Injury		Infantile	Juvenile	Infantile	Juvenile
Relative loss	Verbal	8	1	14	1
	Performance	3	1	5	3

more frequent in cases of infantile injury; but whereas this may not be unexpected with left-sided lesions, it is unexpected in association with right-sided lesions. Comparison between numbers with verbal and performance losses associated with infantile and juvenile injuries to the right hemisphere (in the

second part of Table VI) yields a value of $\chi^2 = 1{\cdot}46$, which does not reach the $P = 0{\cdot}1$ level of significance for the 23 cases. However, it has been possible to add from our records the results of testing a further 42 unoperated children with pneumoencephalographic evidence of unilateral (right-sided) cerebral injury, in whom the age of injury could be ascertained from the history. Using the same criteria as for the operated children, all cases of right hemisphere injury are analysed in Table VIII. For these proportions,

TABLE VIII

TOTALS OF OPERATED AND UNOPERATED CASES FOR RIGHT HEMISPHERE INJURY

Injury		Infantile	Juvenile
Relative loss	Verbal	34	8
	Performance	9	14

$\chi^2 = 9{\cdot}89$ ($P < 0{\cdot}01$), indicating a significant contrast between the type of impairment resulting from right hemisphere lesions sustained in infancy (verbal deficit) and in subsequent years (performance deficit). Returning to the operative series, the records of the group of 11 patients in whom right cerebral injury had occurred in infancy, and who showed a relative verbal loss, were examined for possible association with E.E.G. or pathological abnormalities. Five of these had normal E.E.G.s in the remaining hemisphere; three had grade 1 and three grade 2 abnormalities. Six of these had porencephalic cysts and five had diffuse lesions. (The two cases of Sturge-Weber-Dimitri disease both showed 'conventional', *i.e.*, performance deficit.) There is thus no suggestion that this anomalous verbal impairment with right infantile lesions is significantly associated with any E.E.G. or pathological abnormality.

Dysphasia.—The relative verbal intellectual impairment noted above is a 'high level'—perhaps the highest level—manifestation of a language disability. In many patients there was also evidence of lower level disorder of language, in the form of dysphasia, generally of the nominal type but occasionally including receptive errors. In five of these patients there were also signs of other left hemisphere disabilities such as dyscalculia, constructional dyspraxia, and 'simultanagnosie'. The association of dysphasia with side and age of injury is shown in Table IX: it will be noted that the occurrence of this symptom with right hemisphere injury is almost exclusively in those patients with injuries sustained in infancy, thus agreeing with the evidence of the preceding section. It may further be observed that of the two patients with juvenile left cerebral injury who underwent total hemispherectomy (Cases 9 and 24),

TABLE IX

PATIENTS WITH CLINICAL DYSPHASIA

		Side of Injury	
		Left	Right
Age at injury	Infantile	4	7
	Juvenile	4	1

the first was almost asphasic for some weeks after operation, and showed a fall in I.Q. post-operatively, while the second showed no change in I.Q., in contrast to the general increase after operation seen in patients with infantile injury, together with disappearance of dysphasic symptoms.

Discussion

The data from the present series of patients support the main conclusions which may be drawn from the literature on hemispherectomy. Changes in overall intelligence following hemispherectomy for infantile hemiplegia are generally positive, in contrast to the effects of limited or partial removals. Whereas some of this improvement may be due to practice effects, and to better adjustment to the hospital environment, this only emphasizes the lack of improvement, or deterioration, following partial removals. This evidence, then, supports Krynauw's suggestion that the remaining hemisphere is free to function normally when the abnormal influences of the damaged hemisphere are removed, and among abnormal influences must be included the disturbances associated with epileptic activity.

The few post-operative intellectual losses in our series are all except one (Case 22) in patients who sustained their injury above the age of 1 year, *i.e.*, in patients suffering from juvenile rather than from infantile hemiplegia. As far as can be judged from reports in the literature, this is in keeping with general experience: in cases described as of 'infantile hemiplegia', hemispherectomy has resulted in improvement, while in cases of injury later in life there is some post-operative deficit, although relearning may occur. The one exception to this (apart from the reported dictum of Nielsen) is Obrador's Case 3, in whom the evidence is clearly that the left hemisphere injury was sustained at 5 years of age, and that the consequent aphasia was diminishing following hemispherectomy. Nevertheless, the great majority of reports support Krynauw's second suggestion, that 'adjustment' of hemisphere dominance had occurred before operation, with the limitation that this adjustment is only complete if the injury is infantile. By the end of the first year, it appears likely that the conventional partition of functions into right and left hemispheres has begun, and that subsequent injury to a hemisphere does not entirely

dislodge its functions to the other side, with the result that removal of a hemisphere removes a certain amount of functioning tissue.

Liberated from the influences of the damaged hemisphere, the remaining hemisphere is able to function normally, but it is doubtful whether it can be called 'normal' function: 'supernormal' might be more appropriate. For not only does it perform motor and sensory functions for both sides of the body, it performs the associative and intellectual functions normally allocated to two hemispheres. The remaining hemisphere is dominant with regard to speech, but it is not, as Krynauw suggested, the 'minor' hemisphere which was removed, for 'minor' is conventionally used in relation to language, and comprises a range of cognitive functions associated with pictorial, spatial, and non-verbal material. It is more satisfactory to refer to normal left and right hemisphere functions, and to state that in the infantile hemiplegic these are both mediated by the remaining hemisphere. Following removal of the abnormal hemisphere, this double function is more efficiently performed; but it is interesting to enquire whether there appears to be a limit to the level which it may reach. Our figures (Table III) for the intelligence quotients of the series of patients before operation show a somewhat skewed distribution, with a preponderance of low values. This might be expected, since in many patients cerebral function was grossly disorganized. The post-operative I.Q.s, though generally higher, show an even more skewed distribution, with a greater number of individuals spread over the lower end of the range: this was also found in the cases quoted in the literature (Table I). However, a large part of the 'tail' at the lower end is associated with electrical disturbance (and therefore, possibly, some cerebral damage) in the remaining hemisphere, as shown by the figures in Table X,

TABLE X

INTELLECTUAL LEVEL AND E.E.G. RECORD

Post-operative E.E.G.		Normal	Abnormal (1, 2, or 3)
Post-operative	I.Q. below 60	1	14
	60 and above	12	4

for which $\chi^2 = 12{\cdot}17$, $P < 0{\cdot}001$. Although the numbers are small, it seems likely that the distribution of intelligence quotients may be 'normal', *i.e.*, more or less symmetrical, but limited to an average value in the region of 60, and it may be postulated that this limitation is the result of both left and right hemisphere functions being undertaken by a single hemisphere.

Moreover, our evidence suggests that this limitation may bear particularly heavily upon language, as opposed to non-language, functions. This would perhaps be expected in cases of left hemisphere injury, in which the right hemisphere had to assume unwonted language functions; but the data make it clear that relative language impairment is common also in cases of right hemisphere injury, if this occurred during infancy. It is not possible to state precisely the age at which the earliest language functions are established, normally in the left hemisphere. Griffiths (1954) gives 10 months as the average age at which two words are used, 12 months for three words, and 21 months for the shortest phrases. Probably the most satisfactory criterion for each individual is the age at which he begins to use words; and our results suggest that, while the transfer of intellectual functions from the damaged hemisphere may be complete until that age, there is a restriction on the development of verbal intelligence, so that it does not reach the same level in the individual as does non-verbal intelligence. It is known that verbal ability is often reduced in patients with epilepsy (Halstead, 1957); and it is also probable that a part of the intellectual impairment shown by our patients may have been educational in origin. However, the relative verbal impairment persisted after the removal of the damaged hemisphere, and the post-operative increases, in the few patients who were tested on a comprehensive scale (Table V), was greater on non-verbal than on verbal tests, suggesting that neither epilepsy nor educational retardation are maior factors in determining the verbal deficiency.

Further evidence against the suggestion that the relative verbal impairment is educational in origin is the occurrence of dysphasia and associated 'left hemisphere' disabilities, in cases of infantile damage to either hemisphere, in contrast to the absence of spatial disorientation or other 'right hemisphere' signs. Dysphasia is not a consequence of neglected schooling, and its frequent disappearance following hemispherectomy emphasizes its origin in physiological disturbance. On the other hand, this relative verbal impairment is not found invariably in every patient with infantile hemiplegia. The numbers in the operated series (Table VII) are not sufficient to establish the tendency, and an analysis of further unoperated cases had to be added (Table VIII) to confirm the suggestion. This is in part due to the relative inaccuracy of the distinction between verbal and performance levels when the tests used were not explicitly designed to provide this information. It is probably also due to the inclusion in the groups of cases in which the 'intact' hemisphere was also in fact partly damaged, thus disturbing the expected pattern of development; for example, our two cases of right-sided Sturge-Weber-Dimitri disease both

showed relative performance impairment, as did the patient (Case 2) of Cairns and Davidson (1951).

As stated in an earlier section, this demonstration of limitation of verbal abilities disposes of the question of adjustment of right hemisphere functions: it appears that in cases of infantile injury to either hemisphere these are adequately integrated in the remaining hemisphere, together with left hemisphere functions. Although a few cases of infantile injury have shown a relative deficiency on performance, as contrasted with verbal, tests, this has not amounted to the syndrome of spatial agnosia in contrast to the relatively frequent occurrence of dysphasia in association with verbal deficiency.

Apart from the association of specific types of intellectual impairment with lesions in certain cerebral areas nothing is known of the neurophysiological basis of intellectual functions in the two hemispheres. Consequently, little can be surmized concerning the neurophysiological organization which underlies the execution of the functions of both hemispheres by one hemisphere alone. Whether these functions are distributed in the same antero-posterior locations in the one hemisphere as they would be in their normal hemispheres, whether they occupy relatively discrete regions, or are closely intermingled with other 'contralateral' functions, these cannot be guessed at. Evidently there is a suggestion that some sort of quantitative limit to the capacity of cerebral tissue has been reached. The average intelligence of our patients is well below the normal average; even minor electrical abnormalities in the remaining hemisphere are associated with lower I.Q.s, and there is a tendency, even in those approaching normal I.Q.s, for verbal ability to be reduced, suggesting that this normally requires a greater number of neurones for its expression than do 'non-verbal' performances. Otherwise, it can only be observed that these patients are repositories of cerebral organizations of the greatest interest, further understanding of which will amply repay the most detailed follow-up study.

Summary

A review of published reports suggests that greater improvement in cases of infantile hemiplegia results from complete hemispherectomy than from partial removal. In cases of injury to the left hemisphere, removal has rarely resulted in speech disturbance, and the majority of reports show a rise in intellectual level following removal of either hemisphere.

Comparison of test scores of a series of 28 cases of hemispherectomy with nine of partial removal demonstrates a significantly greater increase in scores in the former group. Taking the cases of hemispherectomy alone, this increase is found to be exclusively in the patients with infantile hemiplegia in the strict sense, *i.e.*, with injuries sustained in the first year.

There is no significant difference in post-operative increase in scores between cases of left and right hemispherectomy in the infantile injury group. Analysis of results shows that greatest improvement is on those patients with normal E.E.G.s in the remaining hemispheres. It is also demonstrated that the majority of patients with infantile hemiplegia show a verbal intellectual deficit, amounting in some cases to dysphasia, irrespective of hemisphere damaged.

It is suggested that these results indicate a limit to the capacity of the remaining hemisphere, imposed by the mediation of the normal functions of both hemispheres by one hemisphere alone.

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FOUR CASES OF CAROTID-BASILAR ANASTOMOSIS ASSOCIATED WITH CENTRAL NERVOUS SYSTEM DYSFUNCTION

BY

ROBERT L. CAMPBELL and MARK L. DYKEN

From the Section of Neurological Surgery in the Department of Surgery and Department of Neurology, Indiana University Medical School, Indianapolis, Indiana, and New Castle State Hospital, New Castle, Indiana, U.S.A.

Various anomalous anastomoses between the carotid and basilar arteries have been reported. Krayenbühl and Yasargil (1957) classify three types. The first and by far the most frequent type is a persistent primitive trigeminal artery. The second in frequency is a persistent hypoglossal artery. The third type is a persistent primitive acoustic artery. We have found only the first type in our angiographic review.

Persistence of the primitive trigeminal artery was first reported by Quain (1844). The first report of angiographic demonstration was not until 1950 (Sutton). In a review of the literature in 1960 (Jackson and Garza-Mercado), only 33 case reports were found. Krayenbühl and Yasargil in their book on angiography describe four cases demonstrated by angiography. Their first case may be an anomaly other than a persistent trigeminal artery, since the vessel appears to originate at the junction of the C1 to C2 portion of the carotid artery. The vessel illustrated in their last case, described in a discussion of an arteriovenous malformation, may be a branch of the external carotid artery. Lindgren (1954) also reproduced angiograms of two cases.

The incidence of this lesion reported in the literature has varied from 1% to 0·001% (Jackson and Garza-Mercado, 1960). As pointed out by Harrison and Luttrell (1953), the true incidence of this lesion is very difficult or impossible to ascertain. We found an incidence of approximately 0·1% at the Indiana University Medical Center, and in a series of 76 angiograms at the New Castle State Hospital, three cases were demonstrated for an incidence of 4%.

Case Reports

Case 1.—A 7-year-old white girl was admitted to the Indiana University Medical Center Riley Hospital on July 5, 1950, because of headaches and unusual behaviour. One week before admission, she suffered progressively severe frontal headaches and epigastric distress. Two days before admission, she became agitated and had intermittent episodes of delirium in which she expressed fear of having her head cut off. She had no fever and no recent upper respiratory symptoms. The gestation period, birth, and neonatal period were uneventful. She weighed 7 lb. at birth. She walked at 9 months and said some words at 18 months. She had a speech impediment, and she was also clumsy and stumbled frequently. She had considerable difficulty in learning at school. For a year before admission, she had had episodes at night during which she would cry and talk to herself. At these times she could be awakened only with difficulty.

On examination, the patient was cooperative, but she was not orientated as to place and time. Her head and eyes were deviated to the left most of the time, but otherwise the general physical and neurological examinations showed no abnormalities. The optic discs appeared normal.

During her stay in hospital, she deteriorated progressively. She developed a mild left hemiparesis and left homonymous hemianopia. Three lumbar punctures revealed a normal pressure, and spinal fluid examination was entirely normal, with a protein content of 15 mg./100 ml. The colloidal gold curve was 1111100000.

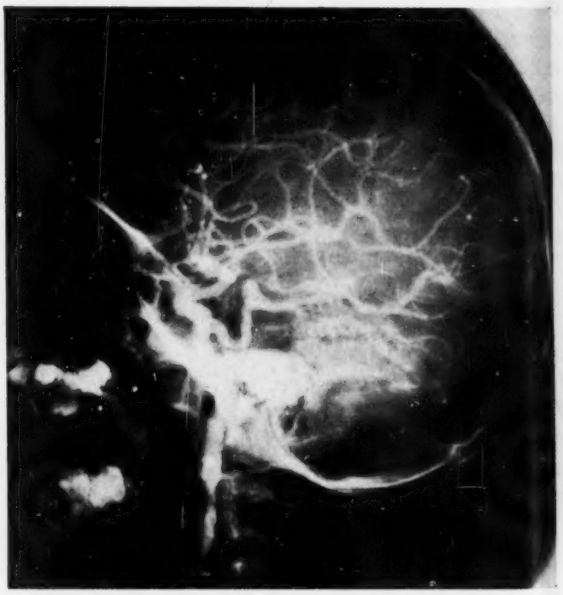

FIG. 1.—Case 1: Lateral angiogram of left internal carotid artery system. Persistent trigeminal artery.

Blood chemistry was normal. Serial electroencephalograms showed high-amplitude, arhythmic slow waves in all leads, maximal in the right fronto-temporal region with evidence of progression. Pneumoencephalograms were normal. Cerebral angiography was normal except for the demonstration of a persistent trigeminal artery on the left (Fig. 1). The patient's parents signed her out of the hospital on August 1, 1959.

Case 2.—A 38-year-old white woman was admitted to New Castle State Hospital in 1951 because of uncontrolled right Jacksonian motor seizures and severe psychotic depression. A history of traumatic birth with subsequent right hemiparesis was obtained from the commitment papers. She did not walk until she was more than 3 years of age. During the first few years of her admission, she would refuse to do anything and sat by herself hour after hour complaining of 'radio voices' cursing her and talking about her. On Rauwolfia and phenothiazine drugs, she adjusted quite satisfactorily to the hospital routine and became a model patient.

On examination, she had a spastic, hyper-reflexic, right hemiparesis with a right-sided Babinski sign. The right extremities and right side of the face were hypoplastic. Position sense was decreased in the right fingers. With the patient sitting, ophthalmodynamometric pressures were 40/110 in both eyes. Psychological testing revealed her intellectual function to be between borderline and mild mental deficiency. There was also evidence of specific organic impairment of the left hemisphere and of affective disturbances.

Repeated electroencephalograms revealed rhythmic 4 to 6 c/s slowing and spikes from the left Sylvian leads.

FIG. 2.—Case 2: Lateral angiogram of right internal carotid artery system. Persistent trigeminal artery.

Bilateral carotid angiography on June 24, 1959, showed a persistent trigeminal artery on the right (Fig. 2). Multiple small angiomas were present in the left middle cerebral artery distribution. Cerebral blood flow by the Kety-Schmidt nitrous oxide technique was measured twice on July 6, 1960. The first test indicated a flow of 40 ml. of blood per 100 g. of brain per minute, and the second 36 ml. of blood per 100 g. of brain per minute.

Case 3.—A 16-year-old white girl was admitted to New Castle State Hospital on September 30, 1958, because of generalized seizures, lapses of consciousness associated with bizarre behaviour, and violent combative behaviour between seizures. When medicated, she had seizures only at night. Seizures began at 30 months of age, following measles and presumed measles encephalitis. They were chiefly psychomotor seizures, but occasionally she had generalized convulsions. She described a brief aura of pain over the forehead and a sensation of spinning inside her head. During these times she was assaultive and destructive and it was a problem to separate the seizure activity from her usual personality. Because she frequently attacked other patients and attendants, she had to be placed in the hospital security ward.

On examination, she was an extremely large, heavy, white girl who was otherwise normal physically and neurologically. Her Wechsler-Bellevue intelligence quotient was 70. Some of the decrease was thought to be the effect of anticonvulsant drugs. Brachial blood pressures with the patient sitting were 110/70 mm. Hg in both arms. Ophthalmodynamometry, with the patient sitting, revealed retinal artery pressures to be 10/65 in the right eye and 30/80 in the left eye. The retinal artery pressures in the supine position in the right eye was 20/72 and 42/75 in the left eye.

Serial electroencephalograms showed generalized rhythmic slowing and multiple spikes, the maximal abnormality being in the right hemisphere. Bilateral carotid angiography was performed on August 2, 1960, and was normal except for a persistent trigeminal artery on the right (Fig. 3).

Case 4.—A 46-year-old white man was first seen on April 12, 1960, at New Castle State Hospital. He had been committed because of mental deficiency from birth, left-sided Jacksonian convulsions for four months, and progressive left hemiparesis for four months. He had been unable to learn at school, but he had made a marginal adjustment working at simple repetitive tasks and living under the supervision of a brother. He could not read or write but could print his name by rote. Four months before admission, he had his first Jacksonian seizure, beginning in the left arm, and afterwards a left hemiparesis. He gradually deteriorated so that two weeks before admission he was unable to walk, could not eat solid foods, experienced considerable nausea and vomiting, and complained of severe frontal and occipital headaches.

A pilonidal cyst was excised in 1944. His mother died at the age of 44 from an unknown cause. She had been confined to a mental hospital because of psychotic behaviour. Both of his parents had diabetes mellitus. Two brothers and one sister were living and well.

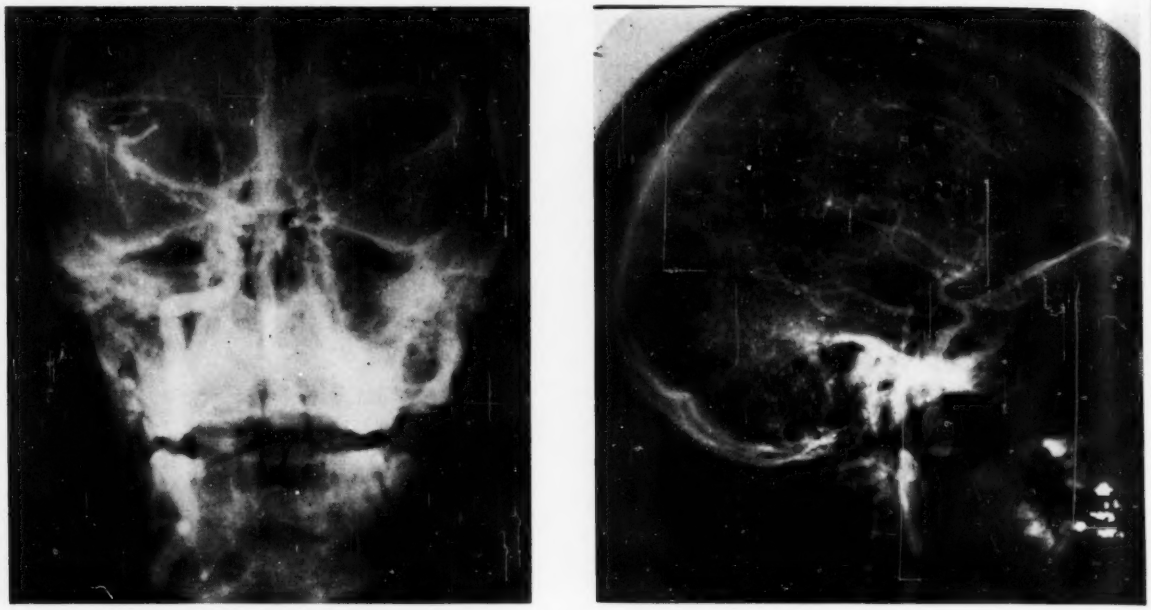

FIG. 3.—Case 3: Right internal carotid artery angiograms. Persistent trigeminal artery.

Physical examination revealed an acutely ill white male, who was obtunded and somnolent. His speech was slurred. He could not walk alone, but when supported he had a left hemiplegic gait. He had a left homonymous hemianopia and bilateral papilloedema. Touch perception was reduced on the left side of the face, and he had a left supranuclear facial paresis. Simultaneous auditory stimulation was ignored, or suppressed, on the left side. The tongue protruded to the left. He had a spastic left hemiplegia, complete in the arm, but with slight function in the leg. His blood pressure was 130/85 mm. Hg and the pulse was 100. On the left side he had hypaesthesia and hypalgesia, suppression of bilateral touch stimuli, absence of position sense, astereognosis and atopognosis. Muscle stretch reflexes were exaggerated on the left side. Abdominal reflexes were absent on the left. The Babinski, Chaddock, and Conda signs were present on the left. The clinical impression was of an infiltrating glioblastoma multiforme of the right hemisphere, with maximal involvement in the posterior

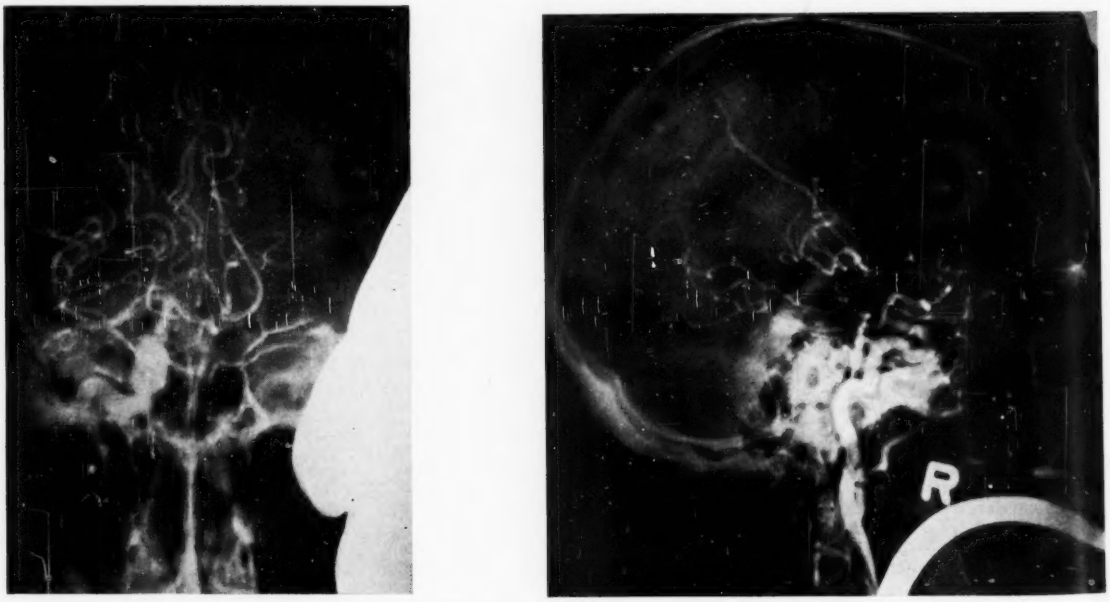

FIG. 4.—Case 4: Right internal carotid artery angiograms. Persistent trigeminal artery and glioblastoma multiforme.

Sylvian region. The patient was transferred to a general hospital. There, bilateral carotid angiograms indicated a massive lesion in the parietotemporal region and a persistent trigeminal artery on the right (Fig. 4).

A craniotomy performed April 14, 1960, revealed an infiltrating glioblastoma multiforme in the right posterior Sylvian region. For internal decompression, the posterior part of the parietal lobe and occipital lobe were removed. On November 19, 1960, when last examined, the patient was essentially unchanged neurologically.

Discussion

The embryogenesis of the trigeminal artery was described by Padget (1948). The anatomical relationships with the third, fourth, fifth, and sixth cranial nerves and the cavernous sinus have been well diagrammed by Harrison and Luttrell (1953). Kepes and Kernohan (1958) found that in about half the cases the artery perforated the dorsum sellae, and in the other half coursed lateral to the dorsum sellae to join the basilar artery. No case has been reported in which this condition existed bilaterally. There is no significant difference in the occurrence on the two sides or between the sexes. This anomaly is frequently associated with unusually small vertebral arteries and a small proximal basilar artery to the level of the shunt. Saltzman (1959) reported eight cases and made an angiographic classification into two types. In the first type the entire basilar artery system distal to the anastomosis was filled through the shunt. This was accompanied by poor filling of the posterior communicating artery. In the second type the shunt angiographically supplied mainly the superior cerebellar arteries, while the posterior cerebral artery received its supply through the posterior communicating artery. The distal end of the basilar artery was poorly visualized in this group. He classified one case as a combination of the two types. Aneurysms not directly related to the shunt are also probably more frequent (Schaerer, 1955; Murtagh, Stauffer, and Harley, 1955).

Various clinical syndromes have been suggested as related to a persistent trigeminal artery. A persistent weakness at the site of the carotid origin of the embryonal trigeminal artery has been suggested as a cause of intracavernous carotid aneurysms and carotid-cavernous fistulas (Sugar, 1951), although from necropsied cases this is probably not the most frequent site (Dandy and Follis, 1941). Only one patient, a 33-year-old woman, had a history of trigeminal neuralgia (Jackson and Garza-Mercado, 1960), but she had evidence of disseminated nervous system involvement, suggesting that the persistent trigeminal artery was not necessarily causally related to the trigeminal neuralgia. Subarachnoid haemorrhage has been purported to arise from this vessel (Kloss, 1953; Saltzman, 1959). Case 2 of Harrison and Luttrell (1953) had a massive intracerebellar haematoma at necropsy, but no mention was made of identifying the bleeding site. To our knowledge, bleeding from a persistent trigeminal artery has not been demonstrated at necropsy.

From the reported cases, it seems apparent that no characteristic clinical syndrome is associated with this condition. However, from our material, it does seem likely that the frequency of this anomaly is greater in patients with retarded mental development dating from infancy. All four of our patients were intellectually deficient, three of the patients being confined to a chronic neurological hospital. In the New Castle State Hospital, a chronic neurological institution, the incidence of the anomaly was three in 76 angiograms. The incidence at the Indiana University Medical Center was only one case in 1,000 angiograms. The probability of the difference in incidence at the two hospitals being significant cannot be evaluated statistically because of the few positive cases. It does seem, however, that the difference is more than coincidental.

Ophthalmodynamometry was performed on two of our patients. Retinal artery pressures were the same in one and significantly different in the other. The difference may be explained by the head of pressure being decreased in the ophthalmic artery distal to a large shunt.

Summary

Four cases of carotid-basilar anastomosis demonstrated angiographically are reported. Although no characteristic clinical syndrome is associated with this anomaly, our cases suggest that there is a higher incidence of this condition in patients with retarded mental development dating from infancy. Carotid-basilar anastomosis is a possible cause of significant differences in retinal artery pressures.

We would like to thank Dr. John Russell for permission to use the angiograms on Case 4.

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DEFECTS IN IDENTIFYING OBJECTS VISUALLY IN A PATIENT WITH CEREBROVASCULAR DISEASE

BY

G. ETTLINGER and MARIA WYKE

From the Psychological Laboratory, Institute of Neurology, London

It has been suggested that the condition associated with disease or injury of the brain in which ability to identify objects is impaired may in certain cases be regarded as a true failure of recognition. Such was the conclusion of Jackson (1876) when he reported a case of 'imperception', of Munk (1877) when he described 'mind blindness' in dogs, of Lissauer (1890) when he distinguished between 'apperceptive' and 'associative' mind blindness, and of Freud (1891) when he proposed the term 'agnosia' for cases having defective 'object-concepts'. Although many authors of the present century (notably Liepmann, 1908; Lange, 1936; Brain, 1941; Hécaen and Ajuriaguerra, 1956) have similarly held that the process of object recognition itself may become disordered, contrary opinions have not been wanting. Thus, Bay (1950, 1953) has argued that in the majority of published cases intellectual deterioration together with subtle sensory changes can be held responsible for defective identification of objects. This view has found wide acceptance (cf. Critchley, 1953; Teuber, 1955), although little evidence in its favour was forthcoming from one recent investigation (Ettlinger, 1956).

It is our purpose to describe a condition resembling visual object agnosia. This report is made for the following reasons: First, the ability of our patient to identify objects by vision, by touch, or by both together, was investigated quantitatively; secondly, his vision was examined with a number of techniques claimed to be relevant to the problem of visual object agnosia; and finally, his intellectual level was assessed by standard psychometric methods.

Case Report

Clinical History.—A storekeeper (F.C., N.H. 84776), aged 59, was admitted to the National Hospital, Queen Square, on January 8, 1960, under the care of Dr. Marshall. Five years previously he had had an attack of vertigo and of numbness of the left side of the face and weakness of the right leg. He made a good recovery and stayed well until February, 1959, when he had another attack of giddiness and numbness of the left side of the body, with weakness of both legs: this again gradually improved. A week before admission he began to have severe headaches, and three days later he complained of visual difficulties. Two days before admission he became confused and had some difficulty in expressing what he wanted to say. He did not take to his bed, nor did he vomit or lose consciousness.

Clinical Examination.—He was a right-handed man with blood pressure of 210/115 mm. Hg. No other abnormalities were found except on examination of the central nervous system.

Although he was moderately disorientated in space and time (but not for person) he was cooperative. He was constantly minimizing his troubles and lacked insight into his difficulties. His identification of objects was defective. There was a nominal dysphasia, he was unable to read, and there was a disorder of writing. However, he was a good subject on neurological examination.

Examination of the visual fields demonstrated a right homonymous hemianopsia. His considerable loss of acuity in both eyes could not be accurately assessed. No abnormalities were seen in the fundi, apart from some arteriovenous nipping. There was no diplopia or nystagmus. Both pupils were small and reacted sluggishly to light. The other cranial nerves were normal.

There was mild weakness and increase of tone of the right arm and leg, with some incoordination. The right plantar response was extensor. There was no sensory abnormality on neurological testing.

The presumptive diagnosis of cerebrovascular disease (brain-stem ischaemia) was made, and he was given anticoagulant therapy.

Investigations.—On January 8, 1960, the urine was normal. Haemoglobin was 16·2 g.%; W.B.C. 5,600 per c. mm.; E.S.R. 2 mm. in one hour. Blood urea was 16 mg.% and serum cholesterol 166 mg.%. The Wassermann reaction was negative in the cerebrospinal fluid and blood. Cerebrospinal fluid pressure was 130 mm. C.S.F. on January 13, 1960. The fluid appeared clear and colourless, no cells were seen, and the protein was 30 mg.%.

A soft tissue swelling in the scalp was the only abnormality on radiographs of the skull (Dr. J. W. D. Bull). An E.E.G. on January 12 (Dr. P. Bladin) gave evidence of 'a structural abnormality on the left side,

which is giving abnormal activity over the whole of the side of the head'.

Progress.—The patient slowly improved during his time in hospital, so that he had very little difficulty in using his right limbs. The dysphasia and field defects persisted. He was discharged on January 7, 1960. Information was obtained in February, 1961, that his condition had deteriorated on account of a further cerebrovascular accident, but no further details are available.

Psychological Examination.—The patient was seen on a number of occasions by different examiners. The results of intellectual testing (Dr. J. McFie) on the Wechsler Bellevue scale (form I) were uneven (Table I). His scores

TABLE I

WEIGHTED SCORES OF F.C. ON SUBTESTS OF WECHSLER BELLEVUE INTELLIGENCE TEST

Subtest	Weighted Scores	Mean for Age 59
Vocabulary	13	9·5
Arithmetic	7	6·9
Similarities	7	7·9
Digit span	6	7·5
Picture completion	9	7·4
Block design	5	6·7

on the vocabulary and picture completion tests were above the average level. Scores on other tests were about average, except in the case of block designs where the score was below this level. His overall intellectual efficiency was found to be about average for his age and this probably represented moderate deterioration from a level that had been higher before his illness. These findings were confirmed by his failure to learn the Babcock sentence in seven attempts and by his poor performance on the Terman memory for designs test and on tests of drawing and construction with match sticks.

His performance on tests of praxis (Professor O. L. Zangwill) was normal except for one instance of misuse of an object. There was no evidence of receptive or expressive dysphasia, but he had mild nominal difficulties and in addition a disorder of writing. His visual orientation in space was preserved.

His performance with other kinds of visual material was also tested (on January 26, 1960). He made eight errors in 12 attempts when asked to give the names of primary colours (not shades) shown to him. These were not entirely dysphasic errors for he still made three errors in 12 attempts when asked to select the names of the same colours from among four alternatives (including the correct name) given him for each colour. Similarly he made four errors in 12 attempts when required to point to colours to command. Asked to give the colours of common objects, *e.g.*, pillar box, sun, coal, salt, etc., he made only one mistake in 26 attempts (giving blue as the colour of the sun). He was correct in six out of nine attempts to find the colour appropriate to an object, *e.g.*, point to the colour of grass, of a roof, etc.

Tested with 10 outline pictures of common objects (taken from the picture vocabulary test of the Terman-Merrill scale) he made nine errors, of which only one was obviously dysphasic. At the same time he was able to discriminate accurately between forms (see section on examination of visual efficiency). Tested with more complex pictures on January 14, 1960, by Professor O. L. Zangwill, he gave very poor descriptions; however, he accurately indicated specific items on request.

Psychiatric Examination.—Dr. R. T. C. Pratt examined the patient on January 26, 1960, when he was found to be disorientated in time and place. His memory for events in his early life was poor. He was thought to be a little too eager to please the examiner, rather than having any tendency to exaggerate his disabilities.

Examination of Visual Efficiency.—In Fig. 1 are shown the patient's visual fields charted on a tangent screen with 1 mm., 2 mm., 1 cm., and 2½ cm. targets. He was also

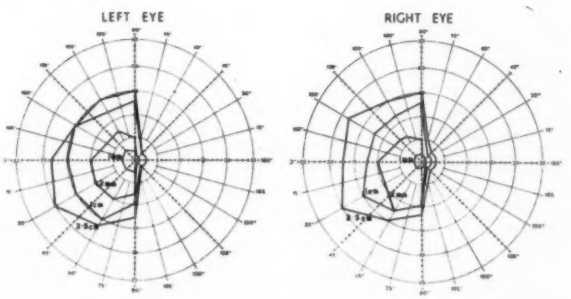

FIG. 1.—Visual fields in F.C. taken with 1 mm., 2 mm., 1 cm., and 2½ cm. targets on the tangent screen.

examined on tests of relative brightness discrimination, flicker fusion, and local adaptation at representative points in his left half visual field and in central vision. (Reasons for using these tests, and a detailed description of the methods of examination are to be found elsewhere, Ettlinger, 1956). The methods and test conditions of the earlier study have been exactly reduplicated in examining our case F.C. Therefore the 'normal' values, presented in the earlier report that refer to the middle 80% of results for the two eyes of the 48 healthy control subjects may also be used here.

The test results at brightness discrimination, flicker fusion, and local adaptation for F.C. are shown in Figs. 2, 3, and 4 in relation to these 'normal' values. The symbol √ in Figs. 2 and 3 refers to thresholds at brightness discrimination or flicker fusion that fall within the 'normal' range of values for a given position in the visual field. The figures preceded by the minus sign indicate in Fig. 2 the degree of impairment of brightness discrimination in F.C. The more negative values indicate a greater degree of impairment (higher thresholds). The figures refer to the number of steps (related to 0·25 log. units of light transmission) that the relevant threshold in F.C. is above the upper limit of the 'normal' values. Similarly the figures preceded by the minus sign in Fig. 3 indicate the degree of impairment of flicker fusion in F.C. Again the more negative values indicate a greater degree of impairment (lower fusion frequencies). The figures refer to the number of cycles per second that the relevant fusion

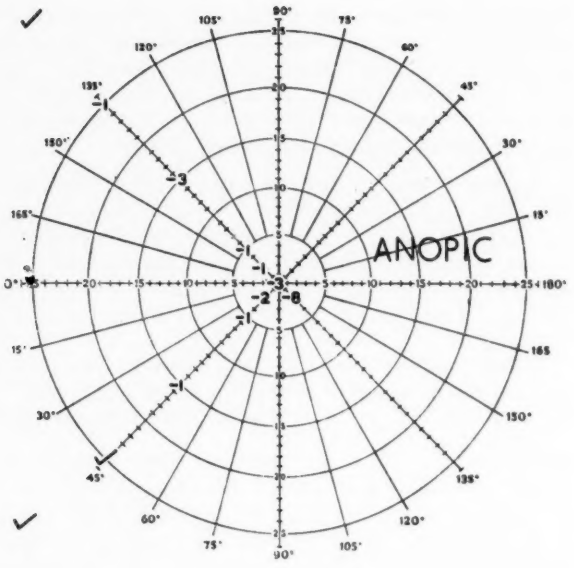

FIG. 2.—Thresholds for left eye of F.C. obtained on a test of brightness discrimination on January 20, 1960.

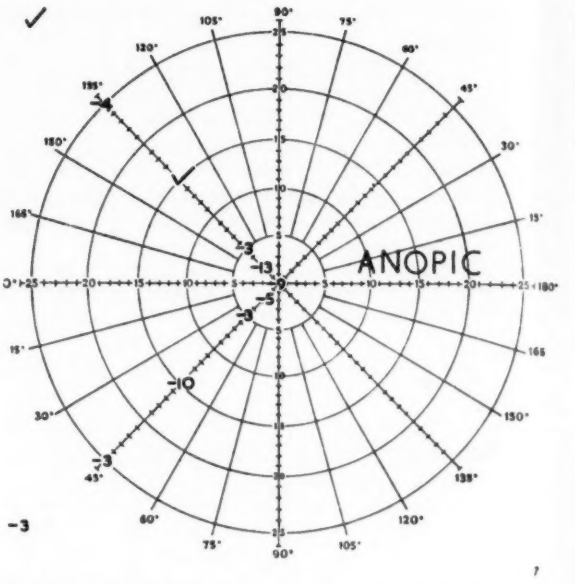

FIG. 3.—Fusion frequencies for left eye of F.C. obtained on a test of flicker fusion on January 21, 1960.

threshold (mean of four readings) in F.C. is below the lower limit of the 'normal' values. In Fig. 4 there are no figures preceded by a minus sign. This is because all the results at local adaptation in F.C. fell within the range of 'normal' values. The figures in this test indicate the duration in seconds of the middle one of three fading times taken at each position in the visual field.

It is seen that there is a mild degree of impairment on tests of brightness discrimination and of flicker fusion (Figs. 2 and 3) but not on the test of local adaptation. In interpreting the results on the former two tests it should be remembered that 10% of values from healthy subjects would be taken to show impairment (and frequently as severe as that in F.C.) merely because the 'normal' limits refer to only the middle 80% of all normal values obtained.

The patient was also tested on January 22 for his ability to match outline shapes, following the procedure used by Brain (1941) to establish the basic adequacy of vision in his case of visual agnosia. For this purpose we used the standardized tests of the Terman-Merrill scale (L) called discrimination of forms, at the four-year level, and pictorial likenesses and differences, at the 4½ year level. The patient made no error in 16 attempts with different shapes. He was also required to match a sample against four alternatives in an unstandardized test of matching irregular forms. There were 10 different sets of irregular forms (each with sample and alternatives) in this test, and he made no mistakes.

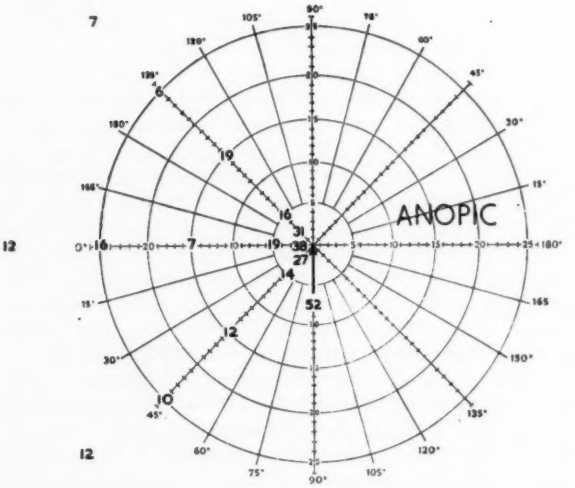

FIG. 4.—Fading times for left eye of F.C. obtained on a test of local adaptation on January 21, 1960.

Experimental Examination of Object Identification

Our patient's faulty identification of objects by vision had been observed immediately on admission, and it had been confirmed during the psychological and psychiatric examinations. Various contributory factors were then investigated. Psychometric testing indicated an adequate level of residual intellectual function despite some deterioration. Visual testing likewise revealed a level of efficiency thought to be sufficient for object perception despite some loss. One problem remained: Was the patient's ability to identify objects by touch genuinely superior to his visual identification? We were able to answer this question as a result of the following investigation.

Twenty-one objects divided into three groups of familiar, less familiar, and unfamiliar objects (Tables II, III, and IV) were presented to the patient. Every object was twice presented for identification under each of three conditions, namely, vision alone, touch alone, or vision

and touch (both hands). Thus our patient made 126 attempts at identification. The 21 objects were presented under the three conditions in random order, and a different random order was used for the second series of 63 attempts.

The patient was asked to name the object. Any response other than the correct name was treated as an error. A time limit of 1 min. was imposed for each object. If his identification was incorrect before the time limit was reached he was asked to guess again what the object might be. The time taken for a correct identification (if less than 1 min.) was recorded with a stop-watch.

Results.—The results of this investigation are shown in Tables II, III, and IV. There were 26 errors with vision alone, 16 with vision and touch, and nine with touch alone (combining the results for all 21 objects). Statistical comparison between the performance under conditions of vision alone and of touch alone indicates that object identification by vision is significantly more impaired than it is by touch ($\chi^2 = 14{\cdot}17$, $P < 0{\cdot}001$).

The similar comparison between performance under conditions of vision alone and of vision and touch together indicates that identification by vision alone is significantly more impaired than it is by vision and touch

TABLE II

IDENTIFICATION OF FAMILIAR OBJECTS

Object	By Vision	Time (Sec.)	By Touch	Time (Sec.)	By Vision and Touch	Time (Sec.)
Spoon	For cooking	60	Spoon	2	Spoon	7
	—	60	Spoon	10	Spoon	2
Cup	Put milk	10	Jug	58	For carrying water	58
	For dressmaking	60	Cup	7	Jug	45
Pen	Pen writer	60	Writing pencil	60	Fountain pen	12
	Fuse tape	60	Fountain pen	4	Fountain pen	4
Glasses	Eye glasses	5	Glasses	5	For putting on	35
	Wristwatch	60	Glasses	3	Compass	45
Glove	A box	15	Glove	7	Spoon	7
	For hands	40	Glove	40	Glove	5
Watch	Not a scarf	60	Watch	12	Wristwatch	4
	Stopper	15	Wristwatch	5	Wrist key	40
Book	Book	15	Book	4	Book	2
	Book	4	Book	10	Key	6

TABLE III

IDENTIFICATION OF LESS FAMILIAR OBJECTS

Objects	By Vision	Time (Sec.)	By Touch	Time (Sec.)	By Vision and Touch	Time (Sec.)
Padlock	A key	60	Cigarette	45	Wristwatch	60
	Lockets	60	Rubber catch	30	A bottle	10
Rubber	Open by key	45	Indiarubber	5	Rubber	4
	For weather	50	Indiarubber	6	Rubber	5
Button	Button	60	Button	15	A mark for clothing	60
	Use with a pin	25	Button	3	Button	5
Scissors	Pen	50	Pair of scissors	15	Scissors	60
	Scissors	40	Scissors	5	Scissors	4
Ruler	In offices	60	Ruler	30	—	60
	A measure	20	You draw with	60	A measure	15
Key	Key	45	Key	6	Key	10
	Staple	59	Key	2	Key	35
Bottle	Button	5	Jar	7	Ink bottle	7
	Key	40	Carrying liquid	50	Bottle	5

TABLE IV

IDENTIFICATION OF UNFAMILIAR OBJECTS

Objects	By Vision	Time (Sec.)	By Touch	Time (Sec.)	By Vision and Touch	Time (Sec.)
Box	Cardboard box	4	Cardboard box	15	A box	15
	Box	2	Box	2	—	60
Wire	Fuse wire	10	Electric wire	10	Flex	55
	Electric tape	15	For wood work	40	—	60
Handkerchief	Handkerchief	7	Piece of cloth	15	Article of dress	15
	Scarf	5	Material	15	Handkerchief	8
Screw	Cigarette	45	Screw	18	Screw	45
	Screw	2	Screw	7	Screw	3
Cottonwool	Cottonwool	15	Use in a . . .	60	Cottonwool	3
	—	60	Cottonwool	3	Being scratch	60
Tie	Tie	4	Piece of cloth	10	Neck tie	5
	Tie	5	Tie	17	Neck tie	4
Paint brush	Painting B	35	Brush for paint	40	Paint brush	40
	Electric plug	60	Brush	10	Brush	5

together ($\chi^2 = 4{\cdot}7$, $P < 0{\cdot}05$). However, the remaining comparison indicates that the difference between identification by vision and touch together (16 errors) and by touch alone (nine errors) is not significant ($\chi^2 = 2{\cdot}79$, $P > 0{\cdot}05$).

A qualitative analysis of the mistakes made by our patient indicates various kinds of error of identification.

Dysphasic Errors.—Dysphasic errors, when the patient failed to give the correct name of an object but nevertheless appeared to recognize it by giving its use or a paraphasic name. There were 12 dysphasic errors when objects were presented for visual identification, six when for tactile identification, and eight when both vision and touch were permitted. When a comparison is made between object identification by vision alone and by touch alone after all dysphasic errors have been excluded, visual identification is still found to be significantly more impaired than tactile identification ($\chi^2 = 10{\cdot}52$, $P < 0{\cdot}001$).

Perseverative Errors.—Perseverative errors were of three kinds. First, there were simple perseverations of the name of an object previously presented and correctly identified. Thus a knife (presented after a fountain pen) was identified as a fountain pen. Secondly, there were more indirect perseverative errors when the name given to an object was related to the use of another object already presented. Thus a paint brush (presented after a piece of fuse wire) was identified as an electric plug. Thirdly, there were repetitive perseverative responses, where a single word, *e.g.*, staple, was repeatedly given at the beginning of various responses to a series of different objects.

Failure in Identification.—The failure of identification was not consistent. There were only a few objects that our patient was unable to identify on both of the two attempts under the same test conditions. We found five such objects on visual testing (padlock, rubber, ruler, bottle, and glove). This result might imply a certain degree of consistency in his failure to identify objects by vision. However, five of these 10 errors, relating to three of the five objects, were dysphasic and not perceptual errors, *e.g.*, a ruler was identified as 'in office' and 'a measure' on successive attempts. Similarly there were three objects (padlock, cup, and glasses) that were incorrectly identified by vision and touch together on both attempts. Three of the six errors, relating to two objects, were dysphasic in origin. There was only one object (padlock) that he failed to identify on both attempts by touch alone. Thus there is little if any evidence to suggest that failure of identification was consistently related to certain particular objects.

We have also been unable to find a meaningful relationship in our case between failure of identification and the degree of familiarity with the objects. These were allocated to their groups (familiar, less familiar, and unfamiliar) by agreement between three examiners on the basis of their frequency of usage. There were fewer (rather than more) errors with the unfamiliar objects than with the familiar ones. Finally, we were able to observe (mainly during less systematic investigations than the one we have described) that on rare occasions the patient was unable to identify an object by touch but gave a correct answer when the same object was soon afterwards presented for identification by vision and touch.

Discussion

We are unable to give further information concerning the extent of the brain lesion in our patient. Though the initial attacks were indicative of a brainstem lesion the subsequent history and physical signs indicated that there was a diffuse pathology, presumably ischaemic in nature and due to cerebral atherosclerosis. However, it should be recalled in this connexion that a right homonymous hemianopsia (with only slight macular sparing) was found to be associated with an extensive restriction of the left homonymous fields. This would imply at least bilateral involvement of the visual system.

We must now consider the relative contributions of confusion, of intellectual deterioration, of dysphasia, and of both visual and tactile sensory changes in the origin of the defective object identification.

The confusion, although not severe, was the salient feature of his condition. In itself, the confusion was not unlike that seen by us in many other cases of organic cerebral pathology. (We have, however, never seen a case of confusion with differential involvement of visual and tactile object identification.) The test results indicated that our patient was of above average intelligence before his illness, but his impairment brought him to a level of intellectual functioning (as assessed by these tests) that was about average for his age. Therefore the confusion, but hardly the dementia, may be considered to have contributed to his failures in object identification.

As well as being confused, our patient was dysphasic. The nature of his errors indicated that he was suffering from a mild nominal dysphasia. However, he was able to obey all commands and comprehend fairly complicated material, and his speech was almost normal in casual conversation. It has been suggested by Pötzl (1928) that the names of colours may be selectively lost ('colour aphasia') as a manifestation of dysphasia but we know of no suggestion more recent than that of Freund (1889) that the names of objects perceived by vision, but not by touch, may be selectively lost in dysphasia. Moreover we found a significant superiority of tactile object identification, even after all such errors as were thought to be dysphasic in origin had been excluded from the analysis. We may therefore suppose that, while some errors of object naming were related to the nominal dysphasia, the defective visual identification was independent of any dysphasic disability.

The residual vision was assessed in a number of

ways. From the fields on the tangent screen it appears to consist of a small area (tunnel vision) comprising mainly the macular portion of the field, somewhat offset to the left. However, it might be recalled that similarly extensive constriction of the visual fields does not necessarily cause faulty object identification (Teuber, Battersby, and Bender, 1960). Other tests either gave normal results for the left half field (local adaptation) or only slight reductions from normal values (brightness discrimination, flicker fusion). Finally, our patient was able to match and compare forms without mistakes. We cannot, therefore, explain the impaired visual identification of objects in this case by reference solely to the defect of vision.

Tactile sensibility was judged to be normal in both hands by the use of the standard clinical test methods.

It could be argued that careful quantitative testing might have revealed some subtle alterations of tactile function but it seems unlikely that such tactile changes could have been comparable in severity to the visual loss. Therefore we may infer on the available evidence that visual function was more severely impaired than tactile.

It is evident that no single one of the factors already discussed, *e.g.*, confusion, dysphasia, visual defect, can account for the impaired object identification. We suggest that the confusion in our case was the predominant determinant of impairment of object identification. This, together with the dysphasia, would account for the appreciable number of errors made during object identification by touch alone, even though on clinical testing there was in this sense modality no loss of (tactile) sensibility. When the confusion and dysphasia were combined with some measure of visual disability, a significantly greater number of errors during visual object identification resulted. When tested under conditions of vision and touch combined, the number of errors was greater than with touch alone. This might be because the visual disturbance served actively to disrupt, instead of merely failing to improve, the performances based upon touch. We therefore propose that the considerable degree of confusion, taken together with some measure of visual disturbance, gave rise to a condition resembling visual object agnosia in our patient F.C. In making this proposal we do not wish to imply that confusion was a major factor in previously reported cases of visual object agnosia. Nor can we, on the evidence available to us, either accept or reject the claims of others to have observed agnosia in the sense of a genuine disorder of recognition. Rather we would stress the importance of the systematic (and if possible quantitative) evaluation of object identification, and also of psychometric and visual performance in cases of suspected agnosia.

Summary

A systematic examination of the defects of visual object identification in a patient with cerebrovascular disease is reported. The patient was required to identify 21 objects twice under three conditions: by vision alone, by touch alone (both hands), and by vision and touch together. He was allowed one minute to give the correct name of each object.

His intellectual functions were also assessed with standard psychometric methods, and his vision was examined on the tangent screen and on tests of brightness discrimination, flicker fusion, and local adaptation. In addition he was given comprehensive neurological, psychological, and psychiatric examinations.

Object identification by vision alone was found to be significantly inferior to identification of the same objects by touch alone or by vision and touch. The relative contributions of confusion, intellectual deterioration, dysphasia, and sensory changes to the impairment of object identification are discussed. It is concluded that confusion together with visual defect caused a condition resembling visual object agnosia.

We are greatly indebted to Dr. J. Marshall for his generous permission to study and report the case of F.C., and for his help in the preparation of this paper. Dr. E. T. O. Slater provided facilities for this work. We also gratefully acknowledge financial assistance to one of us (M.W.) provided by the Mental Health Research Fund. Dr. J. McFie gave valuable help during the investigation. Finally we would like to thank Dr. R. T. C. Pratt and Professor O. L. Zangwill for their helpful comments and suggestions during the preparation of this paper, and Mr. A. H. Pricket, of the Photographic Department, for preparing the figures.

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FLICKER FUSION IN MULTIPLE SCLEROSIS

BY

A. F. TITCOMBE* and R. G. WILLISON†

From the Department of Neurology, United Oxford Hospitals

This paper is concerned with a study of thresholds of critical flicker fusion frequency (C.F.F.) of a light stimulus in patients suffering from multiple sclerosis. The capacity of normal human vision to appreciate the intermittency of rapidly repeated light stimuli is a function of great physiological interest, and it may be impaired by disease at many sites in the visual pathway.

Thus Parsons and Miller (1957) examined cases of multiple sclerosis on the hypothesis that general damage within the central nervous system might be responsible for depressing critical flicker fusion frequency. However, they found the C.F.F. so frequently impaired in their group that they were forced to conclude that retrobulbar neuritis must play a part in damaging its perceptual mechanism. They noted a correlation with pallor of the discs but did not observe cases during the course of retrobulbar neuritis. They suggested the potential value of C.F.F. estimation as a diagnostic test. These observations showed such a striking difference between cases of multiple sclerosis and controls that it appeared profitable to validate them for estimations made with different apparatus, and if possible to confirm their conclusion that depression of C.F.F. was related to the occurrence of retrobulbar neuritis. The relation between C.F.F. and visual acuity and the visual fields in multiple sclerosis is also of considerable interest.

Kurachi and Yonemura (1956) investigated four cases of retrobulbar neuritis and demonstrated the slower rate at which the flickering light was fused subjectively.

Most of the work on flicker fusion has been carried out by ophthalmologists but psychiatrists have also taken an interest in the subject in relation to its impairment in organic psychosis. Phillips (1933) and Riddell (1936) have studied the visual fields by means of flicker from the point of view of the neurosurgeon and this work made it clear that C.F.F. might be depressed by lesions far removed from the retina and the optic nerves. Teuber, Battersby, and Bender (1960) have used the method extensively in their work on visual field defects consequent upon penetrating missile wounds of the brain. Their chief interest was in flicker perimetry and a full summary of their work is given in their monograph (Teuber *et al.*, 1960). Miles (1951) has also described methods of testing the visual field by flicker vision.

Methods

The apparatus employed in this study resembles that devised by Mayer and Sherman (1938) who were probably the first to use a neon indicator lamp, which has the several advantages described by Miles (1950). The apparatus consisted of a beat frequency oscillator, which delivered up to 250 v peak to peak through blocking capacitors to a Mazda type B neon lamp (rating 200-260 v). The oscillator frequency control was continuously variable and covered the range 5-50 c/s with 270° rotation of the control knob. The output waveform was rectangular and was derived from a sine wave so that the on and off periods of each cycle were equal in duration.

The neon tube was mounted at the closed end of a black painted trapezoidal box so that its centre was 45 cm. from the eye. Two hinged metal shutters were used to block the vision in either eye. These shutters could be controlled from the outside of the box so that the testing of binocular and monocular performance could be accomplished without altering the position of the subject. The area of illumination within the bulb remained constant at 2 cm. width, providing a visual angle of close to 2·5° for the visual distance of 45 cm. Though intensity of illumination was not repeatedly measured, the voltage of the oscillator output was frequently checked. The area of the stimulus, according to Hylkema's (1942) figures, was considered adequate to give optimum fusion frequency in the central area and to 'bridge' any but large steep-edged central scotomata that might be present.

The subjects were tested after lying or sitting quietly for 20 minutes to eliminate any possible impairment of performance by physical exertion. The test was performed in a quiet room. The ascending and descending figures for C.F.F. in cycles per second were measured alternately, and our usual procedure was to make three to five 'runs' with binocular vision and to repeat the procedure with each eye alone. Each run consisted of first ensuring that the subject perceived flicker at a low rate,

*Present address: Etherington Hall, Stuart Street, Kingston, Ontario, Canada.
†Clinical research fellow, M.R.C.

increasing the frequency until fusion occurred and then estimating the frequency at which flicker reappeared while the frequency was decreased. The mean of the ascending and descending values separately gave the figures for the range of each eye and these are shown in the visual field charts in Figs. 2-6. The mean of the ascending and descending values together give the figures used in the tables and in the statistical comparisons. The justification for taking a mean of ascending and descending figures is that a single lower normal figure must be defined if the test is to be diagnostically useful. We were aware that the figures for cases of multiple sclerosis and controls would overlap. Because of this, observations made on a single occasion could only be useful in diagnosis when the mean C.F.F. lay below all the control figures. The value of serial observations is referred to later in this paper. Other criteria or determinants as summarized by Landis (1954) were necessarily not determined for each subject because of the need to keep the test a simple one without the complication of multiple factors. However, our figures for C.F.F. in normal subjects fall on the linear portion of the curve relating C.F.F. to intensity illustrated by this author.

Two series of subjects were studied concurrently. The first series of known cases of multiple sclerosis was composed of individuals who were mostly in-patients of the Department of Neurology and totalled 60 cases. The other series of controls was composed of 28 patients with disorders of the nervous system and two healthy workers in the Department. The diagnoses of the in-patients in this series included epilepsy, cervical spondylosis, hysteria, migraine, headache (investigation), cerebral tumour, poliomyelitis, polymyositis, polycythaemia vera, cerebral vascular disease, diabetic neuropathy, closed head injury, and lumbar disc lesion. They were unselected except for the deliberate exclusion of patients suffering from disease affecting vision. The ages of the individuals in the two groups were restricted to the range of 10 to 58 years inclusive. Both groups contained a number of subjects with normal acuity and a number with diminished acuity. In the controls the diminution was due to refractive error, in the multiple sclerosis group to refractive error or to the effects of the disease on the visual system. A proportion of the cases had standard visual fields plotted by one of us (A.F.T.) to confirm defects or scotomata suggested by the history or by the findings on clinical examination, and in general the visual acuity may be accepted as an approximate indication of the function of central vision. Examples of the relation between the visual field and abnormalities of C.F.F. are illustrated later in this paper.

Results

As many other workers have found (Landis, 1954), it has not been possible to determine accurately a single numerical end-point for appearance and fusion of the flicker on descending and ascending scales respectively. The mean of ascending and descending values are therefore used in Fig. 1. It is obvious that there is a notable tendency for the eyes of the patients with multiple sclerosis to have much lower values for C.F.F. than the controls. All the controls have mean values of 29 c/s or higher (mean 35·0 c/s, S.D. 3·4). There can be no doubt about the abnormality of C.F.F. in the eyes at the lower end of the range. It is, however, possible to compare the

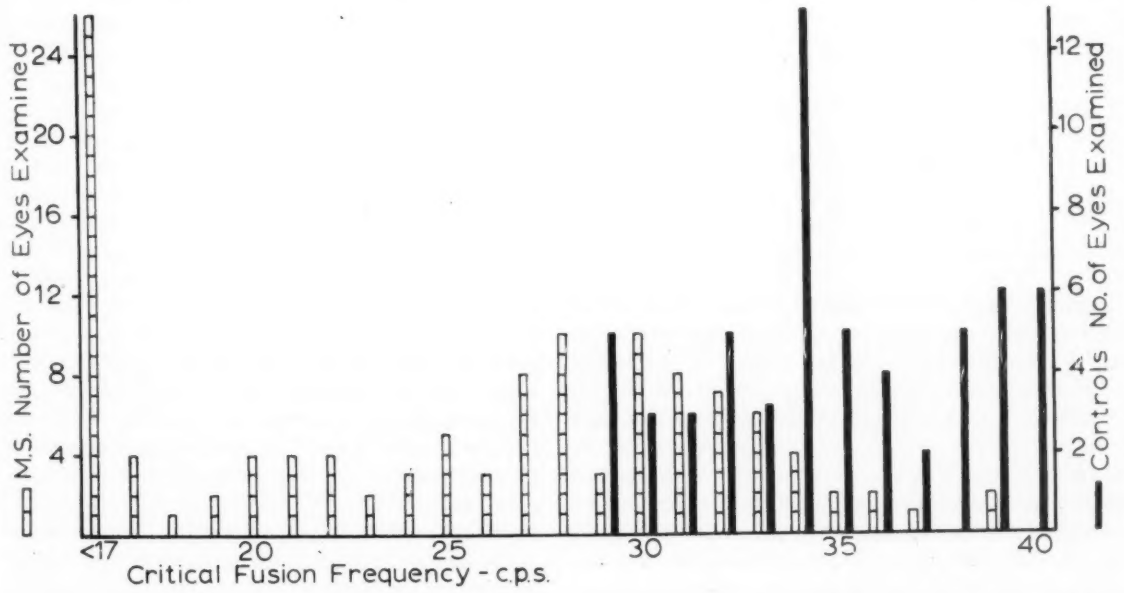

FIG. 1.—Mean figures for C.F.F. in individual eyes of 30 control subjects and 60 cases of multiple sclerosis expressed as the number of eyes showing C.F.F. in each category of whole numbers from 17 to 40 inclusive. The group showing C.F.F. of 16 c/s or less are bulked. Ascending and descending figures were averaged and category chosen as the nearest whole number below or equal to the mean value, *i.e.* 26·7 c/s is placed in category 26 c/s.

two groups statistically. With the assistance of Mr. D. Hewitt two comparisons were made. The first was between 22 control patients with normal visual acuity (6/6 or J1) in both eyes (mean 35·1 c/s, S.D. 3·35) and between 31 cases of multiple sclerosis with acuity of the same standard (mean 27·7 c/s). We considered this to be the most stringent comparison on the grounds that the selection of cases of multiple sclerosis with normal acuity would include those with least affection of the visual pathways. The values for individual eyes were averaged for each patient and the comparisons between the groups made by the χ^2 test. This showed a highly significant difference between the two groups ($P < 10^{-4}$).

The second comparison between eight controls with diminished acuity in both eyes (mean 34·8 c/s, S.D. 3·3) and the cases of multiple sclerosis with normal acuity was also highly significant as would be expected from the small difference between the mean values in the two groups of controls.

Relation between C.F.F. and Visual Acuity.—The statistical comparison was made between cases of multiple sclerosis with normal acuity and the control group because it was evident from the figures that depression of visual acuity and C.F.F. were to some extent related.

TABLE I

VISUAL ACUITY AND C.F.F. IN MULTIPLE SCLEROSIS CASES AND CONTROLS

	Visual Acuity					
	59 Cases of Multiple Sclerosis			30 Control Subjects		
C.F.F. (c/s)	6/6 + J1	< 6/6	Total	6/6 + J1	< 6/6	Total
24 and less	16	31	47	0	0	0
25-28	19	7	26	0	0	0
29 and over	36	9	45	47	13	60
Totals	71	47	118/118	47	13	60/60

Table I shows the relation between 59 cases of multiple sclerosis and 30 control subjects with normal and subnormal acuity in three categories of C.F.F., normal (29 c/s and over), reduced (25-28 c/s), and low (24 c/s and below). It should be noted that values for individual eyes are recorded in this table. The reason for considering values for single eyes is that in any one patient with multiple sclerosis the values for individual eyes may differ considerably, and it is therefore not possible to calculate a satisfactory mean figure for both eyes which could be used in comparisons with controls. This is in contrast to the statistical comparison described above where the problem was the differentiation between the findings in individual cases of multiple sclerosis and control subjects. Table I shows that of the 47 multiple sclerotic eyes with C.F.F. depressed to 24 c/s or less, 16 (34%) had visual acuity of 6/6 or J1. In the group with moderate reduction to 25-28, 19 cases (73·1%) and seven cases (26·9%) had normal and reduced acuity respectively. These figures suggest that although there is a general relation between depression of C.F.F. and visual acuity the two tests of function are not closely linked.

Relation between C.F.F. and Pallor of Optic Discs.—A comparison between C.F.F. and the ophthalmoscopic appearance of the optic discs is shown in Table II.

TABLE II

APPEARANCE OF OPTIC DISCS AND C.F.F. IN 60 CASES OF MULTIPLE SCLEROSIS

	Appearance of Optic Discs		
C.F.F. (c/s)	Pale	Normal	Total
24 and less	45	4	49
25-28	22	4	26
29 and over	26	19	45
Total	93	27	120/120

Table II shows the results obtained in the 60 cases of multiple sclerosis, the values for individual eyes being recorded, in two categories of disc colour (pale and normal) and in three categories of C.F.F. (29 c/s and over, 25-28 c/s, and 24 c/s and less). The discs were examined by us and a definite statement made that they were normally coloured or pale. Table II shows that in general normal discs were associated with higher values of C.F.F. and that pallor was associated with lower values. As the estimation of pallor is largely subjective no statistical evaluation was attempted; neither was any attempt made to grade the degree of pallor of the discs for the same reason. However, from these figures it appears that a pale disc indicates a chance of approximately 2·5:1 against the eye showing C.F.F. of more than 29 c/s. These figures also show that if the number of normal discs in each category of C.F.F. is expressed as a percentage of the total for the line, the proportion falls steeply with decrease in C.F.F. The percentage figures are 43, 15, and 8 in descending order of C.F.F. Furthermore, it will be seen that out of 120 examinations only 19 (15·8%) had normally coloured discs and C.F.F. in the normal range, 29 c/s and over. Although these figures include the subjective errors inherent in the estimation of disc pallor it is of interest to find so many of the cases of multiple sclerosis delineated from the control group by these criteria. Examination of the records for individual cases

shows that only five (8·3%) out of 60 cases had the combination of normal discs and normal C.F.F. of 29 c/s or over in both eyes.

Critical Flicker Fusion and Retrobulbar Neuritis.—The high incidence of depression of C.F.F. in multiple sclerosis and the association of this depression with disc pallor suggest that retrobulbar neuritis may be important in reducing critical flicker fusion. During the period covered by this study three of the cases of multiple sclerosis suffered an episode of retrobulbar neuritis. In one of these patients the C.F.F. fell from 34·5 c/s to 20 c/s, while the visual acuity was initially 6/6 and fell to 6/9. In the second patient C.F.F. fell from 28 c/s to 19·3 c/s and the acuity remained unchanged at 6/9. In the third patient, whose visual fields are illustrated in Figs. 2 and 3 (case R.W.), the C.F.F. was estimated eight days after the onset of retrobulbar neuritis and then two months later. During this period the C.F.F. rose from 17·5 c/s to 27 c/s, and the acuity from 6/9 to 6/5. These observations show a close relation between changes in C.F.F. and retrobulbar neuritis, the depression of C.F.F. in the third case becoming less with improvement in vision.

History of Visual Disturbance and Critical Flicker Fusion.—When the presence or absence of a history of an episode suggestive of retrobulbar neuritis in the multiple sclerosis group is tabulated against C.F.F. in three categories, 29 c/s and over, 25-28 c/s, and 24 c/s and below, there is a definite trend in the figures.

TABLE III

PREVIOUS HISTORY OF RETROBULBAR NEURITIS AND C.F.F. IN 60 CASES OF MULTIPLE SCLEROSIS

C.F.F. (c/s)	History Suggestive of Retrobulbar Neuritis		
	Absent	Present	Totals
24 and less	9	17	26
25-28	7	10	17
29 and above	15	2	17
Totals	31	29	60/60

Table III shows this relation in 60 cases of multiple sclerosis. In this table the value of C.F.F. for the eye showing the lower average value is recorded. As the account of visual disturbance is based on the history from the patient it is not possible in many cases to define whether one or both eyes had been affected in the past; it was therefore impossible to compile the results for individual eyes with confidence in their reliability. The figures indicate approximately equal division of the patients without a history of visual disorder into normal and abnormal categories of C.F.F. In contrast to these, only two patients, in whom a history of visual blurring or loss was obtained, have C.F.F. within the control range. If it is conceded that a history of visual impairment in these cases reflects the incidence of retrobulbar neuritis these figures provide further confirmation of the association with depression of C.F.F. In those cases where there is no history of visual loss, the reduced values of C.F.F., *i.e.*, 28 and below, found in 16 out of 31 cases suggests that there has been an episode or slow progression of retrobulbar neuritis in the past. In this connexion it is of interest that Gartner (1953), in a necropsy study, observed that the incidence of histological changes in the retina and optic nerves was higher than might have been expected from the history given by the patients during life. It is also possible that lesions in other sites may contribute to the depression of C.F.F. in these patients, as suggested by the findings on examination of the visual fields.

Critical Flicker Fusion and Visual Fields.—Five visual field charts are shown (Figs. 2-6) as examples of those encountered in this study. Figs. 2 and 3 show the fields in a patient aged 26 years (R.W.), eight and 44 days respectively, after an episode of retrobulbar neuritis affecting the right eye. Severe depression of C.F.F. (17·5 c/s) is matched by the paracentral field defect to test objects 2/2000 W and 6/2000 R. It will be noted that C.F.F. in the left eye (35·5 c/s), and for binocular vision (35 c/s), remain within normal limits. The visual acuity was only slightly depressed. Forty-four days later the right field has expanded and the C.F.F. has risen. However, it still remains outside the normal range, at a value of 27·5 c/s. The values for the left eye (37·5 c/s) and for binocular vision (35·5 c/s) are only slightly changed.

Fig. 4 (M.C.) suggests that central vision is important in determining C.F.F. These fields were recorded in a patient of 48 years and they show a right upper quadrant defect in both eyes. Central vision is intact and C.F.F. is only slightly below normal (28·5 c/s left, 28 c/s right).

Fig. 5 (C.D.) shows the fields in a 30-year-old man. There is a mild left upper quadrant defect in both eyes with preservation of C.F.F. within the normal range (31·5 c/s left, 35·5 c/s right). The fields in this case and case M.C. (Fig.4) suggest that small lesions in the optic tract may cause only limited disorder of the perceptual mechanism of C.F.F.

Fig. 6 is taken from a 26-year-old man. He had suffered several episodes of visual loss before the C.F.F. was estimated and had at one time had a lesion in the optic chiasm. Despite visual acuity of

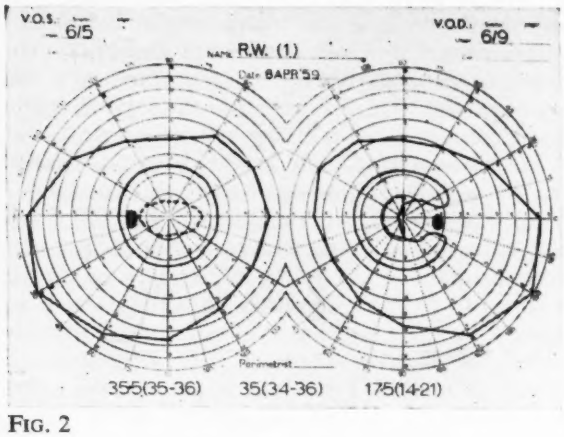

FIG. 2

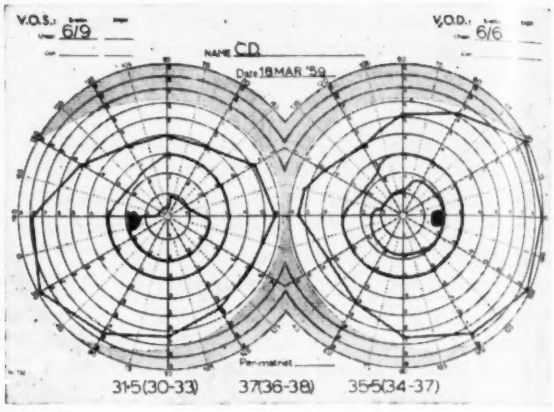

FIG. 5

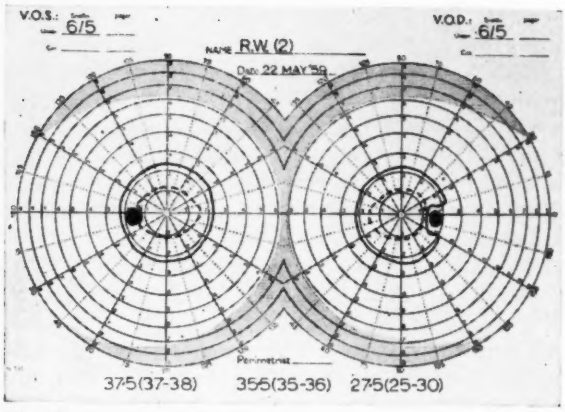

FIG. 3

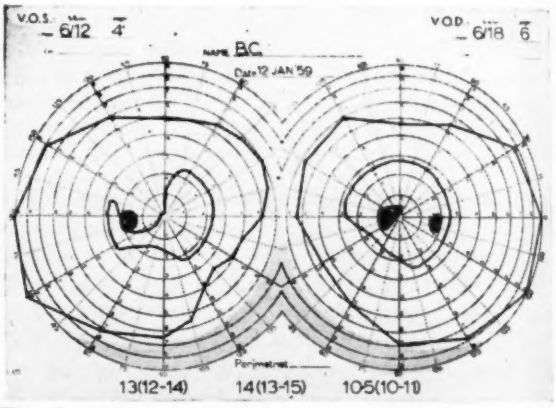

FIG. 6

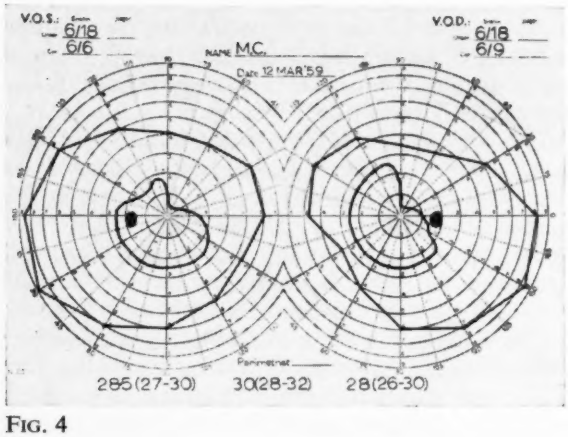

FIG. 4

FIG. 2.—Visual field of Case R.W. (1) eight days after onset of retrobulbar neuritis affecting the right eye. In this diagram and in Figs. 3-6 the outer solid line indicates the peripheral field to a test object 3/330 white. Inner solid lines indicate the field estimated on the Bjerrum screen with an object 2/2000 white. The interrupted lines indicate fields estimated with a test object 6/2000 red. The figures under each diagram give the mean C.F.F. (range in parentheses) and those placed centrally refer to binocular estimation of C.F.F.

FIG. 3.—Case R.W. (2). As in Fig. 1, 44 days after retrobulbar neuritis showing recovery of the visual field and of C.F.F. in the right eye.

FIG. 4.—Case M.C. to show minimal impairment of C.F.F. in relation to a mild right upper quadrant defect with little encroachment on central vision.

FIG. 5.—Case C.D. to show mild quadrantic defects with preservation of C.F.F. within the normal range.

FIG. 6.—Case B.C. showing severe deficit in central vision in both fields associated with impairment of both visual acuity and C.F.F. in a patient who had suffered severe retrobulbar neuritis in both eyes.

6/12 (right) and 6/9 (left) the depression of C.F.F. was very severe (10·5 c/s left, 13 c/s right).

(A more comprehensive study of the relation between C.F.F. and the visual fields is in preparation by one of us.)

Discussion

There is no doubt that the groups of cases of multiple sclerosis and control subjects differ statistically to a highly significant degree. This applies particularly to those subjects with normal visual acuity. From the point of view of diagnosis it is important to set a lower limit to the normal range below which estimations may be considered abnormal with confidence. Fig. 1 showed that only five out of 60 control eyes had C.F.F. of 29 c/s, there being none below this level. Taking into account the standard deviation of our observations, we regard 28 c/s as being abnormal with fair certainty using this technique. We wish to emphasize that this applies only to estimations made with this design of apparatus and that values obtained with different light intensities and areas of illumination might well differ by many cycles per second. Indeed Landis (1954) warned, 'the fact that marked intra- and inter-individual variations do occur in C.F.F. measurement should serve as a cautionary warning to anyone working with any variety of C.F.F. phenomena'.

The estimation of C.F.F. with this technique is simple, provided that precautions are taken to maintain uniformity of the conditions of the test. It appears clear from this series that retrobulbar neuritis is the main cause of depression of C.F.F. in multiple sclerosis but factors such as the effects of exertion, body temperature and ambient temperature, intercurrent infections, and smoking have not been studied. All these are known to cause subjective visual disturbance in patients with multiple sclerosis and they might be expected to influence critical flicker fusion.

While the comparisons made in this investigation have been made between control subjects and patients in whom the diagnosis of multiple sclerosis had been made with certainty on clinical grounds, it is suggested that the estimation of C.F.F. may be useful in displaying abnormality of visual function in patients with clinical symptoms and signs suggestive of multiple sclerosis but who give no definite history of retrobulbar neuritis.

The question of the relation between binocular and monocular values of C.F.F. is a complex one and requires further study. Both in controls and in cases of multiple sclerosis the binocular values are often slightly higher than the monocular values. Because depression of C.F.F. may be confined to one eye in the cases of multiple sclerosis and the chief interest of the study lay in the relation of C.F.F. to other tests of monocular vision, we have not considered the phenomenon of binocular improvement in this paper. It would also be of interest to measure the visual acuity by more accurate techniques (Walsh, 1957) and compare the results against C.F.F. findings.

Summary

A simple means of testing flicker fusion frequency is described. Results in 30 control subjects and in 60 patients with multiple sclerosis are presented. They indicate that multiple sclerosis is often associated with depression of critical flicker fusion frequency in one or both eyes. The depression appears to be related to the occurrence of retrobulbar neuritis.

We wish to thank Dr. Ritchie Russell, Dr. C. W. M. Whitty, Dr. J. M. K. Spalding, and Dr. Honor Smith for permission to study cases under their care, and Mr. D. Hewitt, of the Department of Social Medicine, Oxford University, for his invaluable help with the statistical evaluation of the estimations.

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THE EFFECT OF ANXIETY ON TIME JUDGMENT AND TIME EXPERIENCE IN NORMAL PERSONS

BY

SAMUEL I. COHEN and ALEXANDER G. MEZEY*

From the Institute of Psychiatry and the Maudsley Hospital, London

This investigation was prompted by the frequent observation that in normal persons awareness of the passage of time varies with the emotional state. Certain physiological changes, occurring spontaneously (François, 1928; Hoagland, 1933; Lecomte du Noüy, 1936) or induced by drugs (Bromberg, 1934; Wolf, 1952; Goldstone, Boardman, and Lhamon, 1958), are associated with abnormal time judgments. The well-known physiological accompaniments of emotion (Altschule, 1953) might be responsible for a disorder of the 'physiological clock' (Gooddy, 1958 and 1959), *i.e.*, of the bodily functions habitually serving as time mechanisms.

The methods used for testing judgment of time have been critically discussed by Clausen (1950) and the relevant literature reviewed by Wallace and Rabin (1960). We have selected tests to measure (*a*) the judgment of time in the absence of external clues (time production), and for this we used a method of counting aloud (Steinberg, 1955); (*b*) the ability to reproduce given time intervals without reference to their duration; (*c*) verbal estimation of the duration of given intervals; (*d*) judgment of the duration of long and actively spent intervals. Observations were made before the subjects were due to speak before a critical audience, an experience which they regarded as emotionally disturbing. Significant changes in adrenocortical function have been reported in comparable situations (Connell, Cooper, and Redfearn, 1958).

Our aims were to investigate (1) whether anxiety is associated with an impairment of time judgment, resulting in a discrepancy between personal (internal or psychological) and actual (external or clock) time; (2) whether there was any relationship between subjective distortions of time-perceptions and the results of objective tests.

The Experiment

The subjects were 24 doctors (21 men and three women), working at the Maudsley Hospital. Their ages ranged from 27 to 36 years, with a mean of 30. They were in normal health.

Testing took place in a quiet and relatively isolated room, the subject and one experimenter being present. Each subject was tested twice, once during a normal working day and once about an hour before he was due to speak in public. In half the subjects the control test preceded the experimental one and in the other half the order was reversed. The two tests were separated by 10 to 42 days. The testing procedure, identical on both occasions, was as follows:

Counting (Production).—The subject was asked to count aloud at one count per second. The time taken to count to 31, *i.e.*, his estimate of 30 seconds, was measured by stop watch. The test was performed twice successively (subtests 1 and 2).

The subjects were asked to complete the Maudsley personality inventory; the results of this were required for a different investigation, and it was inserted at this point to provide an interruption of about 10 minutes between the main parts of the test.

Tapping (Reproduction).—An electrically driven automatic time signal, emitting a brief pip every three seconds, was used for this test. The subject was told that after hearing five consecutive pips he would be asked to reproduce the intervals separating the pips by tapping on the table; the time from the first to the eleventh tap, *i.e.*, his estimate of 30 seconds, was measured with a stop watch. This was immediately repeated (subtests 1 and 2).

The subject was asked to estimate the interval between pips after he had listened to another sequence of five (verbal estimation). The subject was asked how he was feeling. After his answer he was asked whether he was feeling relaxed or tense. The subject was asked how time seemed to be passing (normal, slow, or fast). Finally, the subject was asked to estimate the total time he had been in the room. This time was compared with the actual time spent, as measured with a stop watch, usually about a quarter of an hour.

Results

The results for time production by counting are shown in Table I. The means, standard deviations, and range of results were very similar on both occasions. The mean time taken to count out what

*Assisted by a grant from the Ford Foundation.

TABLE I
COUNTING AND TAPPING

	Control		Emotion		Control		Emotion	
	1	2	1	2	1	2	1	2
Mean (seconds)	39·8	40·3	40·2	40·3	29·5	29·7	30·7	29·9
S.D.	11·6	13·5	12·9	12·9	4·7	3·1	4·7	3·9
Range	22·7-75·0	23·1-74·8	12·3-66·0	14·3-67·0	21·0-43·2	24·3-37·0	22·8-35·7	23·0-40·0
$r_{1,2}$	+0·95		+0·97		+0·86		+0·57	

was thought to be 30 seconds was in fact almost exactly 40 seconds; only four subjects took less than 30 seconds. The wide variation between individuals is reflected in the standard deviation and the range of results. This is in contrast to the remarkable consistency of each individual's performance in subtests 1 and 2 on each occasion; the correlation factor between the two subtests was equally high each time. However, the correlation between the results of the two testing occasions was very low.

Table I shows all results for time reproduction by tapping. On both occasions the mean time taken to reproduce the 10 three-second intervals was almost exactly 30 seconds. The smaller variation in time judgment between individuals is shown in the figures for standard deviation and ranges. In a state of anxiety the correlation coefficient between subtests 1 and 2 was + 0·57 as against + 0·86 obtained in the control test. This difference is statistically significant ($t = 2{\cdot}1$; S.E. $= 0{\cdot}308$; $P < 0{\cdot}05$).

Table II shows that the mean, standard deviation, and range of estimations of the three-second interval were very close on both occasions, with a high correlation (+ 0·8) between the two sets of results.

TABLE II
INTERVAL ESTIMATION

	Control	Emotion
Mean (seconds)	3·6	3·7
S.D.	1·0	1·1
Range	2-6	2-6

When tested before they were due to speak in public, 20 of the 24 subjects said they were either anxious or tense; only two rated themselves similarly in the control observations.

Before speaking in public, seven subjects said that time seemed to pass faster than normally, and five said it seemed to pass more slowly. These 12 all rated themselves as anxious or tense. There was no relationship between the way in which the passage of time appeared to be altered and the direction of the deviations in any of the individual test results. In the control tests all 24 subjects said that time was passing normally.

The actual time spent in testing was nine to 19 minutes in the control and eight to 15 minutes in the emotional setting, which illustrates the more hurried performance in the latter situation. Table III shows the results, the estimated time being given as a percentage of the actual time spent. Means and standard deviations are similar, but the range slightly narrower under emotion.

TABLE III
DURATION OF EXPERIMENT

	Control	Emotion
Mean (percentage of actual time)	110	109
S.D.	28	25
Range	62-200	78-174

Discussion

Distortions of time-sense are common in many forms of mental disturbance, including anxiety. They may represent a form of depersonalization-derealization, and this may underlie our finding that half of our subjects, when rating themselves anxious or tense, had a subjectively altered experience of time, without objectively demonstrable differences in time judgment.

The tendency to count slowly compared with clock time is in accord with previously recorded observations (Steinberg, 1955). Two observations emerged from the tapping experiment: (1) The judgments were much more accurate than in the other experiments. A reason for this may be that in this experiment the subject's notion of clock-measured time is not introduced and cannot therefore interfere with his judgments. (2) When the subjects were anxious the test-retest reliability was significantly impaired, so that this test would seem to be more sensitive to anxiety than the others. A possible explanation is that the influence of subtest 1 on the performance in the immediately following subtest 2 ('anchor' effect) is disrupted by anxiety.

Summary

The effect of anxiety on the time experience and time judgment of 24 normal subjects was measured.

The anxiety was caused by the anticipation of speaking before a critical audience. The tests included production, reproduction, and verbal estimation of time intervals ranging from one second to 19 minutes, and were supplemented by introspective statements about time experience.

Our findings were: subjective distortion of time experience occurred in half of our subjects. There were no corresponding objective changes in time judgment. Judgments in the time reproduction experiment were the most accurate but their reliability was impaired during anxiety.

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THE MAY (1961) ISSUE

The May (1961) issue contains the following papers:—

Intrathecal Tuberculin in Disseminated Sclerosis: The Immunological Aspects. Honor V. Smith, Iwan E. Hughes, and George Hunter

Therapeutic Trials in Multiple Sclerosis: Preliminary Report on Effects of Intrathecal Injection of Tuberculin (P.P.D.). Henry Miller, D. J. Newell, Alan Ridley, and Kurt Schapira

Gamma Globulin Studies in Multiple Sclerosis and Their Application to the Problem of Diagnosis. Kurt Schapira and Dorothy C. Park

The Stiffness of Spastic Muscle. John Foley

Intense Rigidity of the Arms Due to Isolation of Motoneurones by a Spinal Tumour. Geoffrey Rushworth, W. A. Lishman, J. Trevor Hughes, and D. R. Oppenheimer

The Effect of the Removal of the Nucleus Dentatus on the Parkinsonian Syndrome. Szabolcs Tóth

Some Experimental Observations on the Action of Intravenous Hypertonic Urea in Dogs, with Particular Reference to Plasma Volume and Tissue Urea Changes. Shedden Alexander, J. C. Eaton, and H. J. Freedman

On the Coexistence of Epileptic Seizures and Abnormal Involuntary Movements. Jerzy Chorobski and Tadeusz Bacia

Narcolepsy in Identical Twins. Norman W. Imlah

Observations on the Carotid Bruit. W. B. Matthews

Herpes Zoster and the Landry-Guillain-Barré Syndrome. J. D. E. Knox, R. Levy, and J. A. Simpson

Hypersominia in Dystrophia Myotonica. J. C. Phemister and J. M. Small

The Fiction of the "Gerstmann Syndrome". Arthur L. Benton

Vinyon "N" as Dural Substitute and its use in other Neurosurgical Conditions. Paul Teng

The Case Notes of the National Hospital for the Paralysed and Epileptic, Queen Square, London, Before 1900. Richard A. Hunter and L. J. Hurwitz

Book Reviews

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1961, **24**, 269.

THE EFFECT OF DEPRESSIVE ILLNESS ON TIME JUDGMENT AND TIME EXPERIENCE

BY

ALEXANDER G. MEZEY* and SAMUEL I. COHEN

From the Institute of Psychiatry and the Maudsley Hospital, London

There is some experimental evidence that normal and morbid emotion differ in the nature of physiological changes associated with them (Mezey and Coppen, 1960). The following investigation was undertaken to find out whether the experience and judgment of time in morbid emotion is different from that in normal anxiety.

The Experiment

The subjects were 21 patients (12 men and nine women), suffering from an affective disorder in which depression was the dominant feature. Their ages ranged from 25 to 63, with a mean of 44. All were physically healthy and afebrile. They were tested shortly after their admission to the Maudsley Hospital during the period of preliminary clinical study and before active treatment was started. After recovery, or improvement sufficient for discharge from hospital, the patients were retested; 15 patients received electroconvulsive treatment, and at least 10 days separated the retest from the last treatment. The interval between the two tests varied from four to nine weeks.

The testing procedure was identical with that used in a previous experiment and described in detail on page 266 asking the patient to count at intervals of a second and his estimate of 30 seconds was measured. For time reproduction he listened to a sequence of pips at three-second intervals and was then asked to tap at the same rate; the time taken to tap out 10 intervals was measured. He was asked to estimate the duration of the three-second interval between pips, and the total duration of the experiment, usually about 20 minutes. His assessment of his emotional state and his subjective experience of the passage of time were also recorded. In addition, the patients completed the Maudsley personality inventory; the relationship between time judgments and the personality factors measured by this questionnaire will be reported elsewhere.

*Assisted by a grant from the Ford Foundation.

Results

The results for time production by counting are shown in Table I. When depressed, the mean time taken to 'produce' 30 seconds was almost 40 seconds; however, the apparent improvement in time judgment with recovery was not statistically significant. Standard deviations and the range of results were slightly larger in the depressed state.

Table I shows the results for time reproduction by tapping. As in the previous test, the mean results obtained on recovery from depression were closer to the 30 seconds' actual duration; the difference between the results on the two occasions was not significant. Standard deviations and the range of results were also larger during depression.

Table II shows that the mean verbal estimation of the three-second interval was very accurate during depression and a full second longer on recovery, but the difference between the two was not significant. The standard deviations and the range of results were very similar on both occasions.

Table III shows the estimated total time of the experiment expressed as a percentage of the actual time, which varied from 12 to 30 minutes. The difference between the means is not significant. The standard deviations were larger and the range of results considerably wider in the depressed state.

TABLE I
COUNTING AND TAPPING

	Depressed		Recovered		Depressed		Recovered	
	1	2	1	2	1	2	1	2
Mean (seconds)	40·3	37·7	35·6	34·4	25·7	25·7	29·4	29·2
S.D.	19·3	18·7	12·8	13·4	9·0	5·3	6·1	4·2
Range	18·8-97·4	16·4-77·0	18·0-68·2	15·3-70·0	13·8-51·4	17·0-35·6	20·0-45·0	21·0-37·0
$r_{1,2}$	+0·92		+0·98		+0·87		+0·65	

TABLE II
INTERVAL ESTIMATION

	Depressed	Recovered
Mean (seconds)	3·2	4·2
S.D.	2·1	2·8
Range	0·5-9	1-10

TABLE III
TOTAL DURATION

	Depressed	Recovered
Mean (% of actual time)	90	85
S.D.	37	25
Range	17-154	30-110

When depressed, 16 patients reported a slowing, and some even an apparent arrest of the passage of time, describing this experience in evocative terms ('Every hour seems a year to me'; 'It is terribly slow —interminable'; 'Time? It is standing still'.) Three patients felt that time was passing normally and only two that it was passing faster than usual. On recovery from depression 15 patients reported a normal, two a slower, and four a faster subjective experience of the passage of time (Table IV). This high incidence of slowing down of the experience of time in the depressed state was statistically highly significant.

TABLE IV
SUBJECTIVE EXPERIENCE OF TIME

	Depressed	Recovered
Normal	3	15
Slow	16	2
Fast	2	4

Discussion

Distortion of time sense is a not uncommon symptom in psychiatric illness, particularly in affective disorders. Relatively few papers have been devoted to a clinical description of it (Straus, 1928; von Gebsattel, 1928; Lewis, 1932). Others have commented on its relevance to the existential experience of the patient, or on its psychopathological implications (Minkowski, 1929; Binswanger, 1933; Schilder, 1936; Straus, 1947; Tamarin, 1960) and three authors (Bouchard, 1926; Giehm, 1931; Lewis, 1932) have approached the phenomenon experimentally.

In so far as one can generalize from our small numbers, about three-quarters of patients suffering from depressive illness feel that time is passing more slowly than normal and this feeling tends to disappear on recovery. It is probably a particular aspect of retardation (Lewis, 1932). In normal anxiety the direction of the altered experience of time is variable, slow or fast (Cohen and Mezey, 1961), and may be related to depersonalization. Normal anxiety and morbid depression thus have different effects on subjective time experience.

In objective tests time production and time reproduction tended to be more accurate after recovery. In these tests, and also in the estimation of the total time of the experiment, there was a tendency to a narrower range of results and less individual variability once the depression had lifted. However, the difference between the results on the two occasions never reached significance level. Our inability to detect an alteration of time judgment in depression is in agreement with earlier work (Bouchard, 1926; Lewis, 1932).

The effect of depression on the time experience and time judgment of 21 psychiatric patients was investigated. The tests included production, reproduction, and verbal estimation of time intervals ranging from one second to 30 minutes, and were supplemented by introspective statements about time experience. Our findings were that depression is associated with a slowing down of the experience of time. Time judgment is not significantly impaired in depression.

We wish to thank our colleagues for acting as subjects in the first experiment and Dr. R. H. Cawley for his advice on statistical aspects.

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THE ABSORPTION OF TRI-ORTHO-CRESYL PHOSPHATE THROUGH THE SKIN OF HENS AND ITS NEUROTOXIC EFFECTS

BY

P. GLEES and W. G. WHITE

From the University Laboratory of Physiology, Oxford

General and neurotoxic effects of ingested tri-ortho-cresyl phosphate *(TOCP) in man and animals have been described in detail for the last 20 years. We refer here only briefly to the clinical literature where TOCP was implicated, such as Jamaica ginger paralysis in America (Aring, Bean, Roseman, Rosenbaum, and Spies, 1941; Aring, 1942); the massive intoxications by engine oil at the beginning of the Second World War in Germany (Creutzfeldt and Orzechowski, 1941-43), in Switzerland (Moeschlin, 1952), and recently in Morocco (Smith and Spalding, 1959). Experiments on animals to study the dosage and the histology have been carried out by Barnes and Denz (1953), Cavanagh (1954), Hierholzer, Noetzel, and Schmidt (1957), Glees (1957), Silver (1959), Bondy, Field, Worden, and Hughes (1960), and Glees and White (1960). While these studies have clarified the amounts of TOCP necessary for producing toxic effects, little attention has been paid to the possibility that TOCP might be absorbed by the skin so readily that it would also damage the central nervous system. The likelihood of TOCP coming in contact with the skin in industrial workers is great as it is contained in small amounts in some plasticisers, lubricants, and petrol additives, as well as in certain lacquers. That skin absorption is possible was demonstrated by Hodge and Sterner (1943) using radio-active TOCP compounds. We decided therefore to study in a systematic way the amount of TOCP to be painted on the skin of hens necessary to cause symptoms, and to investigate neurohistologically the degree of nerve fibre degeneration.

Methods of TOCP Administration

Pure TOCP was painted on the combs of 32 mature hens and cocks, ranging from 3 to 5 kg. in weight, with the help of a tuberculin syringe, bringing the nozzle in direct contact with the comb. In a single session 0·2 ml. could be spread on this skin, and an interval of one day was observed for additional paintings. In eight hens, oral doses of TOCP, varying from 0·1 ml./kg. to 0·3 ml./kg., were administered, to compare their effects with the cutaneous application.

After an initial trial period, when we used varying quantities of the substance, we soon found that 0·1-0·2 ml. TOCP/kg. painted on the comb regularly produced functional and neuropathological signs of intoxication and 0·05 ml. TOCP/kg. produced neuropathological damage only.

Clinical Signs

A few days after TOCP had been applied the chicken showed a decrease in appetite lasting several days before returning to normal. The loss of appetite is followed by a characteristic head shaking, which comes in bursts lasting several minutes. On the average, 15-20 days after painting, the hen is found sitting down but can get up when prodded. At the same time the appetite is again greatly reduced or abolished. The gait becomes stepping, and the hen is incapable of a balanced posture. Closer examination shows that the extensors of the toes are mainly involved. The toes are held in a typical claw-like position while the flexors, when tested by extending individual toes, are very strong. When the bird is thrown into the air it can fly very skilfully, and the tail and wings fan out in the appropriate way to facilitate landing. However, as the toes do not spread out due to weakness of the extensors, the bird falls over. The head is held erect throughout the illness and the bird follows visual stimuli attentively and reacts normally to sound. The exertion of flying causes the bird to breathe unduly heavily. After a dose of 0·2 ml. of TOCP or more, the paralysis will eventually be followed by a respiratory failure, which is instrumental in bringing about the death of the animal, unless a cortisone preparation is given (Glees, 1960).

Neurohistological Techniques

The animals were, after varying intervals, deeply anaesthetized with nembutal and perfused with formol saline. The extent of perfusion necessary for good fixation can be judged from the appearance of the comb, which becomes quite pale, and the stiffness of neck and legs. Waiting for an hour after perfusion the central nervous system and the peripheral nerves were dissected

*Tri-ortho cresyl phosphate is also known as tri-ortho-tolyl phosphate.

carefully and suitable levels immersed in Marchi (Swank-Davenport modification) fluid. The blocks selected for silver stains were fixed for a further week. The silver impregnation methods of Glees and Nauta (1955) were used.

Neurohistological Findings

In order to avoid a repetitive account of the histology, we have selected from our material three hens, Nos. 28, 51, and 42.

Hen 28: 0·05 ml. TOCP/kg.—The hen painted with a total dose of 0·2 ml. (body weight 4·1 kg.), survived 53 days, and did not show signs of intoxication at any time. Marchi preparations of transverse sections of the spinal cord show a moderate degree of degenerating fibres in the ventromedial area of the cord, and longitudinal sections of this region demonstrate the breaking up of the myelin into large and small droplets (Figs. 1 and 2). Medullary levels show a similar small involvement of the spino-cerebellar tract.

Hen 51: 0·1 ml. TOCP/kg.—The total dose given was 0·37 ml. (body weight 3·7 kg.). The hen was badly paralysed after 13 days and was killed 26 days after painting. The slides of lumbar and medullary levels show a considerable area of degeneration (Fig. 3). Hens which had 0·2 ml./kg. or more show a further increase in degeneration both in Marchi and in silver preparations.

All chickens who have a positive Marchi staining show, when impregnated with the Nauta and Glees technique, disintegrating axones (see Fig. 4), confirming Cavanagh's findings (1954). In addition to axonal changes very distinct synaptic degeneration was found in a circumscribed area of the grey matter (Glees, 1961).

Glial reactions become obvious only in the later stages of degeneration and appear to be secondary to axone fragmentation (Fig. 5). This is clearly seen in hen 42 (body weight 3·4 kg.) which was given 0·7 ml. TOCP and killed 55 days later.

Discussion

Cutaneous application of TOCP, 0·1 ml. or more, causes in hens a characteristic clinical and neuropathological picture. The latter is limited to a selected area of the cord and peripheral nerves are not involved. This clearly demonstrates that pure TOCP can penetrate through the skin of the comb

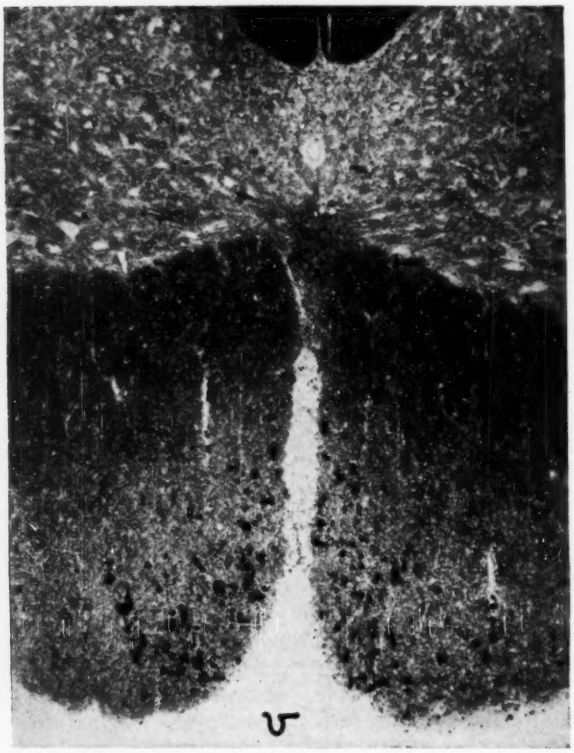

FIG. 1.—Hen 28. Transverse section through lumbar cord. V = ventral. On either side of the ventro-medial fissure myelin degeneration can be seen (Marchi × 35).

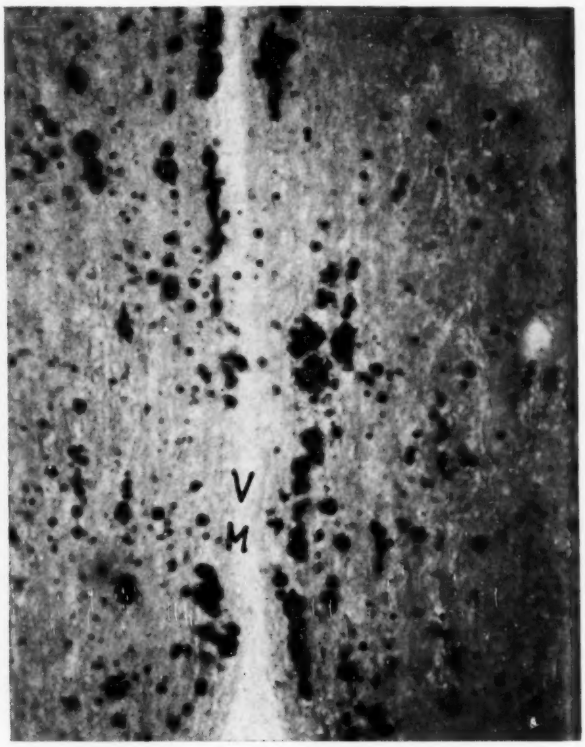

FIG. 2.—Hen 28. Longitudinal section of lumbar cord. V.M. = ventro-medial fissure (compare with Fig. 1). Large myelinated fibres are shown in the process of disintegration (Marchi × 420).

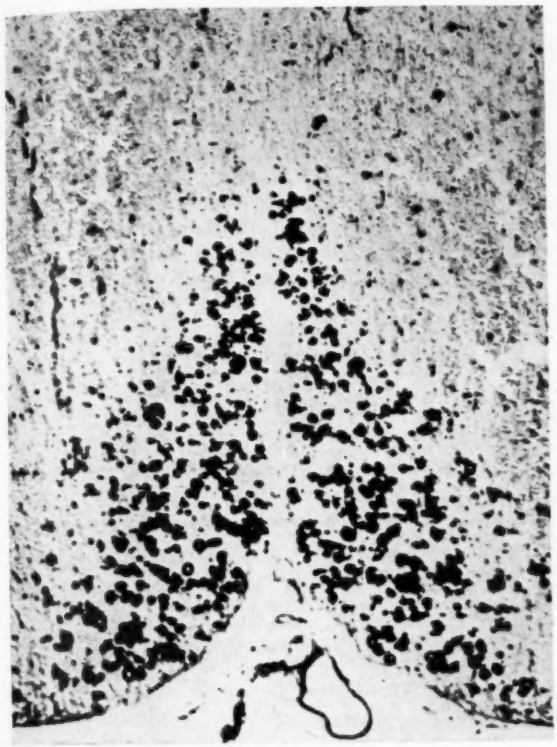

FIG. 3.—Hen 51. The Marchi degeneration at lumbar level on either side of the ventromedial fissure is much more pronounced than in the case of hen 28 (Marchi × 100).

FIG. 4.—Hen 35. Longitudinal section through the ventromedial area of the spinal cord, lumbar level. Note the disintegration and fragmentation of axones (Nauta × 420).

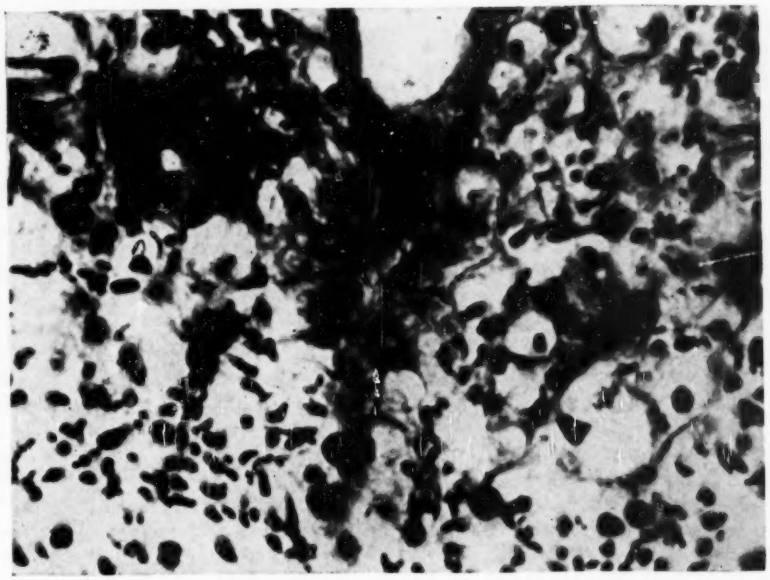

FIG. 5.—Hen 42. Section of ventromedial portion of lumbar cord showing glial proliferation (right side of picture), also myelin and axone degeneration (left side of the picture shows normal axones) (Glees × 420).

producing a similar disease to that which has been described for TOCP taken by mouth. The fact that TOCP can be absorbed rapidly by the skin has been shown by radioactive TOCP applied to the skin and its excretion by the kidney measured by the Geiger-Muller counter (Hodge and Sterner, 1943). These authors were surprised by the rapidity and quantity of absorption, which reached high values after one hour. Doses as small as 0·05 ml./kg. are still capable of causing tract degeneration in the cord although no functional abnormalities could be observed. As TOCP is retained in the tissues (visceral organs and brain) (Hodge and Sterner, 1943), it is possible that the continuation of such a small dose of TOCP as 0·05 ml. might result in an obvious state of toxicity.

Summary

Functional and neurohistological studies in 40 chickens painted on the comb with 0·1 ml. TOCP/kg. or more show a characteristic paralysis of leg extensors and selected spinal tract degeneration of both myelin and axone.

Even a single dose of 0·05 ml. TOCP/kg. is capable of causing a small amount of nerve fibre degeneration in the anterior medial tract of the cord.

No degeneration of peripheral nerves of the leg was detected with the dosage used.

We would like to thank Mr. P. P. Hopf, B.Sc., for the supply of pure TOCP and his interest in this problem, and Mrs. M. Krebs, B.Sc., M.Sc., Miss F. Greene, Mr. B. Sheppard and Mr. H. Hauffe, B.A., for technical assistance. This investigation was partly supported by grant No. 259 from the National Multiple Sclerosis Society, and partly by a grant from Messrs. A. Boake, Roberts and Co., Ltd., and the Geigy Co. Ltd.

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A CASE OF 'PURE' WORD BLINDNESS

BY

A. KREINDLER and V. IONĂSESCU

From the Institute of Neurology, Bucharest

The concept of 'pure' word blindness is still a matter of controversy. Some authors maintain that it is a selective asymbolia (Holmes, 1950; Symonds, 1953; Brain, 1955) while others (Critchley, 1953) consider it to be an aphasic disorder. Beringer and Stein (1930) attribute its mechanism to some pathological functional lability of the visual system. Martin (1954) assumes that it is due to visual disorientation, and Warrington and Zangwill (1957) ascribe it to disorders of ocular motility.

Alexic disorders have been named either according to semiotic criteria, for example, pure word blindness, pure optic alexia, or to pathological criteria related to the site of the lesion, for example, subcortical word blindness (Wernicke, 1886) or occipital blindness.

At the same time, a review of the literature on this subject illustrates the great variety of techniques used for clinical examination, and the lack of a standard clinical examination of alexia has made a synthesis of this problem as well as drawing general conclusions very difficult (Leischner, 1957).

We consider this report of a case of 'pure' word blindness to be of some interest: it was studied by means of various classical tests and also by a standard examination for alexia worked out at the Institute of Neurology, Bucharest, by Weigl and Fradis (1960).

Case Report

V.M., aged 62, right-handed, was admitted on September 27, 1960, complaining of difficulty in reading and of paraesthesia in the right upper extremity.

The patient had suffered from lues in 1916 for which he had been incompletely treated. For the past two or three years he had been found to be hypertensive, with maximal values of 20 to 21 mm. Hg.

The patient had only an elementary education. Since his youth and until his admission to hospital he had worked as a commercial employee in various concerns (cereals, textiles, metallurgy). His heredo-collateral antecedents were not significant.

The patient complained of paraesthesia in the right upper extremity, for four or five weeks. Subsequently, he suddenly experienced difficulty in reading words and letters and, at the same time, a narrowing of the visual fields. (He was no longer able to see clearly to the right.) His writing had not changed, but in current speech he sometimes had difficulty in finding the right word. Despite this symptom he was still able to make himself understood to those around him, but on account of the visual disturbances and difficulty in reading he had to give up his work. He was admitted to a provincial hospital where a Wassermann test in the blood was found to be positive.

On examination there was a right homonymous hemianopia but macular vision was preserved (visual acuity 1). Examination of the fundus oculi showed a normal disc and second-degree arteriosclerosis of the retinal arteries. There was slight anisocoria, the right pupil being larger than the left, but both pupils reacted promptly to light and convergence. The eyeballs moved normally. Nystagmiform movements were found on looking to the right. There was right central facial paresis without any other cranial nerve disturbances. Power, tone, and coordination as well as reflexes were normal. No superficial or deep sensibility disorders were noticed.

The patient was well orientated in time and space, as well as concerning his own person and his environment. He had a lively and practical intelligence, promptly answering the examiner's questions and displaying a normal capacity for abstraction. His ideas were coherently and logically associated without interpretative tendencies. Attention was good and prompt, all tests being correctly performed. Fixation and recall memory for recent events were slightly impaired. His memory for remote events was particularly good. His affect was unchanged. No pathological disorders were observed in the volitional sphere.

His blood pressure was 17/9 mm. Hg but there were no other pathological visceral changes. The Bordet-Wassermann and cytochol tests were strongly positive in the blood. Cerebrospinal fluid contained 4·6 cells/c.mm., albumin 0·38 g. per 1,000 ml., Pandy and Nonne-Appelt tests positive, Wassermann reaction negative. Glycaemia was 1·50 g. per 1,000 ml. (three repeated determinations), the E.S.R. 25 mm./hr., 55 mm./two hours. A routine urine examination failed to disclose glycosuria. The blood urea was 0·20 g. Radiographs of the lungs were normal. A simple cranial radiograph showed marked diploic vascularization, perisellar ligamentous calcification, a normally calcified and located pineal gland, and partial calcification of the falx cerebri. An E.E.G. disclosed a flat tracing which was desynchronized in all leads. Hyperpnoea did not alter the tracing. There were no signs of a focal lesion.

Language Examination

Spoken Speech.—Spontaneous, narrative, and dialogue speech was fluent and coherent, the patient being only very rarely at a loss for a word. Morphological and syntactical constructions were adequate and no paraphasia was found. Repeated speech was well preserved; the patient repeated all the words he was given without making a single mistake. To test automatic speech, the days of the week and the number of days in a year were given correctly. He showed no deficit in understanding spoken language. He performed both the simple commands and the complex ones, composed of two, three, or even four commands, including the Pierre-Marie test and Head's tests, without error. In Kleist's tests the patient readily identified all the words which were pronounced correctly and distinguished all words which made sense from those which did not. When naming objects and animated things, he displayed a slightly increased latency in his answers but considerably shorter than in aphasia.

Standard Examination for Aphasia.—The patient named correctly the 20 pictures of objects and animated things contained in the standard test (Kreindler and Fradis, 1957). Only by a very painstaking test, when another 28 pictures of animated things and of objects were used, was there a slight anomia; for instance, the patient was unable to name an ashtray, a pad, a brow, a fox, as well as certain colours (see colour gnosia).

Written Language.—The patient's reading of individual letters, both silently and orally, displayed important disturbances. Printed or handwritten letters were only identified with difficulty and he made many mistakes. His mistakes in recognizing the 25 letters of the alphabet varied also in relation to the type of letter (Table I).

TABLE I
READING OF LETTERS

Type of Letter	No. of Letters Recognized out of 25 Shown
Printed (capital) letters	14 (56%)
Printed (small) letters	13 (52%)
Handwritten (capital) letters	10 (40%)
Handwritten (small) letters	15 (60%)

Consequently, the most important disorder in this group of tests was detected in reading handwritten capital letters, probably due to the fact that these letters are not much used in current writing.

To test his ability to recognize the categories of written symbols the patient was given printed and handwritten letters mixed with numbers and punctuation marks and was asked to sort them (Leischner's test, 1957). His sorting according to categories was faultless.

Standard tests of alexia according to Weigl and Fradis (1960) were also given. (1) The patient was given a model of a letter and told to find the identical letter in a group containing numerous written letters. He grouped the identical letters without making a single mistake. (2) He was given a model of a printed letter and told to find the corresponding handwritten one. In only seven out of 17 instances was the patient able to pass this test correctly. (3) A letter was read to the patient and he was asked to find it in a group of written letters. He found 14 out of 17 letters, *i.e.*, he scored a better percentage rate (82%) compared with simple reading of letters (40-60%). This auditory facility operated also in reading words.

There was complete verbal alexia (word blindness) affecting both oral and silent reading. The patient was not able to read a single word, no matter how simple. Attempts were made to unblock alexia by the unblocking tests worked out by Weigl and Kreindler (1960).

Visual Unblocking of Concrete Words.—(1) The patient was given a written word which represented the name of an object commonly used or of a phenomenon of nature. At the same time he was shown several pictures. Then he was requested to point to the pictures which the word conveyed. He wrongly read 10 out of 20 words. (2) The patient was shown a picture and asked to designate the adequate word out of several written words. He correctly read 16 out of 20 words.

Auditory Unblocking.—(1) The patient was told a word and instructed to read it from a group containing several written words. He carried out this test faultlessly, making no mistake either as regards concrete or abstract words. (2) A written word was shown to the patient and he was asked to identify it out of several words heard by him. He correctly named 18 out of 20 words in the category of concrete words and all abstract words.

Reading of Sentences proved to be impossible. Facilitating (unblocking) auditory tests were carried out according to the model described for verbal alexia. (1) The patient was told a sentence and instructed to read it out of several written sentences. He was able to read eight out of the nine concrete sentences and four out of the five abstract sentences. (2) He was then shown a written sentence and asked to identify it amongst several sentences heard by him. He recognized all the nine concrete sentences which were given to him to read. Visual and auditory unblocking have a transient effect on lexia, which is strictly limited to their period of action. Reading of punctuation marks was good.

Tactile reading (dermolexia) was also good. The patient was able to read all the letters and words which were written on his skin.

Proprioceptive reading was unimpaired. The patient was able to identify by means of muscular proprioception all letters given to him. He could also correctly read the letters and words written by passive movements, the examiner leading the patient's hand.

Reading of figures and arabic numbers was less impaired than that of letters or words. He correctly read the numbers from 1 to 10, but misread numbers formed of several figures; there were more mistakes in the reading of complex numbers (Table II). The reading of arithmetic signs was correct. Reading of figures and Roman numbers unfamiliar to the patient was inconclusive.

The patient was able to tell the time correctly without making a single mistake.

Function of Numbers.—The patient correctly understood the number series from 2 to 2, 3 to 3, 4 to 4, 5 to 5, and was able to count faultlessly from 1 to 100. When

TABLE II
READING OF ARABIC NUMERALS

Presented Number	Numerals Read
25	25
76	75
64	64
125	105, 125
304	504, 304
601	201
156	156
1,256	1,436
6,290	5,260, 5,290
14,352	14,525
26,340	23,604

counting backwards, from 100 to 1, he skipped the numbers from 30 to 18, but read the rest correctly.

To test his classification of numbers with regard to their value, the patient was given a couple of numbers having near values and instructed to say which was the bigger and which the smaller. He performed this test correctly.

He gave correctly the number of days in the year, in a week, the number of weeks in a month, in a year, and the number of months in a year, making but a single mistake, *i.e.*, he stated the number of days in a year to be 330 instead of 365.

In giving the number of members of his family and of objects in the room he made no mistake at all.

Mental arithmetic was performed quite correctly, very few mistakes being recorded in elementary addition, subtraction, multiplication, or division (out of 30 tests only four were wrong.)

In solving simple written arithmetical problems involving the same tests, he made 12 mistakes (out of 30), which could be readily accounted for by the reading difficulty for figures.

Writing.—The patient was asked to write a letter to his wife. He wrote well, intelligibly and comparatively fast but with a few mistakes consisting in the omission of some letters at the end of the words, and of some punctuation marks. In a letter consisting of 42 words he omitted four letters and five punctuation marks.

The patient wrote all the letters of the alphabet to dictation without a mistake. He correctly wrote the words dictated to him, excepting some small errors of the type mentioned for spontaneous writing. He was unable to read what he had written spontaneously or to dictation.

Copied writing was greatly altered, even unintelligible. The patient obediently copied in an '*écriture servile*' the letters and words given him as a model. To copy a word took about three times as long as to write the same word to dictation. A comparison between writing to dictation and copying, the same words being used for both, clearly showed the maintenance of his ability to write to dictation and the severe impairment as regards copying (Fig. 1). Writing of punctuation marks showed no pathological changes. Writing of arabic figures, spontaneously and to dictation, was faultless. Copying arabic figures showed far less disturbance than copying letters or words. The patient could copy eight out of 10 figures. The patient's written arithmetic proved satisfactory. Left-hand writing revealed nothing abnormal.

Writing with closed eyes was possible and showed no qualitative differences compared with writing with open eyes.

Rhythm Tests.—The patient was able faultlessly to perform various simple rhythm tests such as ////, //|//|//|, /|//|/|, /|//|//|/|//|//|.

Music.—The patient could not read or write musical notes. For this reason, investigation as regards music was very summary. He could distinguish between folk music, classical, and modern music, and was able to recognize different folk tunes as well as some operatic airs.

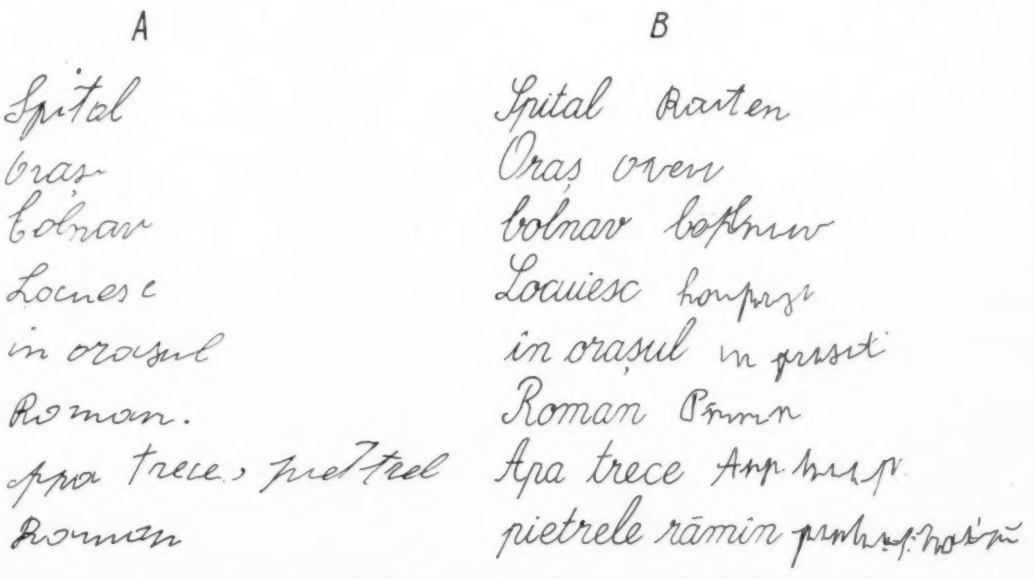

FIG. 1.—A. Writing to dictation. B. Copied writing (the same words as in writing to dictation).

He would not sing either spontaneously or when requested, stating that he was unable to do so. He unsuccessfully whistled a familiar tune.

Praxis.—The tests for ideatory, ideomotor, facio-bucco-lingual praxis and dressing praxis were performed normally.

Constructional Praxis.—The patient correctly drew a square and a circle but failed to draw a rectangle correctly. He initially outlined a triangle, then drew a rectangle only with the assistance of the examiner. He could not draw geometrical forms in perspective, *i.e.*, instead of a cube he would draw a square. This deficit concerning perspective drawing was again encountered in other drawings (house). He erroneously drew a star with five corners, a bicycle, a man (Fig. 2), a car, but correctly drew a cross and a zigzag line.

The blindfolded patient was instructed to touch various geometrical objects (rectangle, circle, etc.) and then to draw them (Halstead's test). He correctly performed this test. Copied drawing revealed the same deficit in reproducing the element of perspective. Copied drawing was better than that done to command (excepting the sketch of a man, Fig. 2).

The patient was unable to build a cube by means of matches, either to command or if given a model. Nor could he assemble a single puzzle, either with or without a model (Koh's test).

Gnosis.—Gnosis of objects and pictures was very good. The patient was able to recognize the component elements of some complex pictures, some of which had symbolic value: a young man leading an assault of a fortress with flying colours; a sinking ship; a preaching priest; Jesus Christ's descent from the cross.

Right-left differentiation was performed perfectly, both as to his own person and to that of the examiner. Digital gnosis was correct as well as autotopognosis and stereognosis.

Gnosis and Naming of Colours.—On the colour chart he correctly indicated the white, black, green, blue, and red colours. He mistook yellow and also violet. The other intermediary colours were indicated correctly. The naming of 'concrete' colours (blue like the sky, green like the grass, red like blood) was imperfect.

From a series of samples he was told to select the main colours (Holmgreen's test), and chose them at random, in an unsystematic way. He made no mistake in selecting the samples but only chose some of the most vivid colours, refusing to indicate the remaining colours or being unable to find them. He thus assembled only two or four samples each of the main colours. Spontaneous grouping was very unsystematic, the patient grouping heaps of colours that clashed, for instance, green and pink. When grouping was done by the examiner according to basic colours, the patient firmly refused this way of grouping, saying 'different colours have been mixed up, they are not the same, that won't do' but then agreed, saying, 'still, according to the colours it is all right'.

Colours were named correctly only for white and black. The other colours were named erroneously, for instance, green was called light brown, yellow—grey, red—yellow, light blue—grey.

Spatial Gnosis.—The patient had a good orientation as regards immediate visual space and the usual visual space (house, hospital); here he made no mistakes, but he was unable to draw a map of the country, nor could he correctly locate the main towns on the map done by the examiner. He stated he had never been able to do this. He drew a rudimentary and incomplete plan of the room in which he was examined. Distances were estimated correctly (the size of the room, of the house, and the distance between various objects). The patient did not display signs of unilateral spatial inattention (he correctly counted beads uniformly scattered, halved a line correctly, and adequately bisected an angle). He had no difficulty in orientation and in fixing his gaze on a moving object.

Clinical Course

The patient was given antiluetic treatment and anticoagulant drugs (heparin) associated with a hypotensive

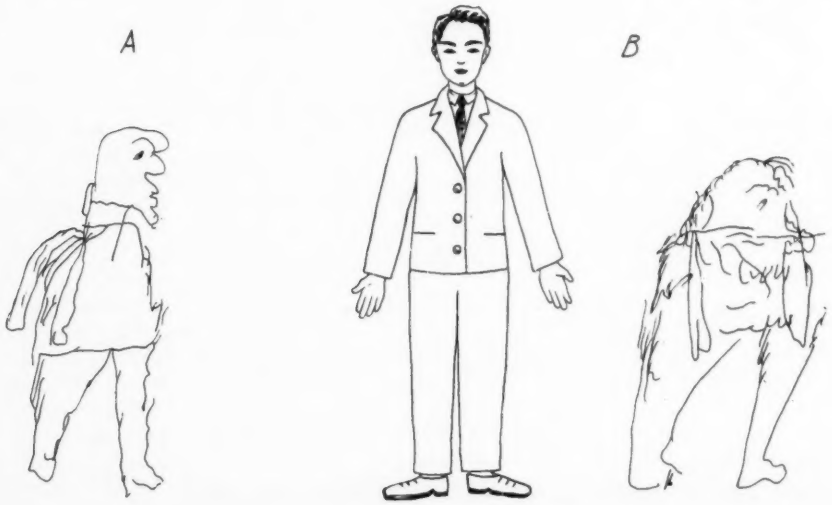

FIG. 2.—A.. Drawing to command: sketch of a man (notice that both arms were placed to the left according to the unimpaired visual field). B. Copied drawing of a man was infinitely worse than the same drawing done to command.

drug (Serpasil). A month later, he had improved in reading letters (he was able to read 18 letters) and words (he could read some simple words), the disturbances as regards colours had improved and the slight anomia had disappeared.

Discussion

As has been stated by many authors, the terms 'pure' word blindness and 'pure' alexia are inadequate. In all cases reported in the literature as well as in our own case, alexia is associated with other symptoms, such as, for instance, right homonymous hemianopsia, colour agnosia, spatial agnosia, constructional apraxia, anomia, dysgraphia (affecting copying of script), dyscalculia. This association is attributable to the fact that the area subserving reading is common to that subserving other higher functions (colour gnosis, spatial gnosis). Yet, it is no less true that alexia, as in this case, may dominate the clinical picture with a minimal involvement of spoken speech and hence makes it possible to separate alexia from aphasia (Casey and Ettlinger, 1960).

Most authors consider 'pure' word blindness to be the result of a brain injury. Pathological findings are indicative of this. Dejerine (1892) found lesions located at the base of the cuneus and involving the lingual and fusiform gyri. In a case of 'pure' word blindness, Hinshelwood, Macphail, and Ferguson (1904) found an extensive lesion of the left occipital lobe expanding down to the occipital pole. Ross (quoted by Leischner, 1957) carried out an anatomico-clinical study in a case with word blindness and right homonymous hemianopsia in which he found a softening of the grey matter in the left occipital lobe; the gyrus angularis was intact. Pötzl (1919) likewise found left occipital injuries (gyrus lingualis) and lesions of the splenium corporis callosi in two cases of 'pure' word blindness. The same author (1927) reported another case of an 82-year-old alcoholic man, who presented with two episodes of right hemiparesis, right homonymous hemianopsia, and verbal alexia. His patient was able to read letters. Pathological findings disclosed two softenings on the internal face of the left occipital lobe, one of which involved a major part of the gyrus lingualis and penetrated into the lateral ventricle. The other lesion involved a small part of the left calcarine fissure (the portion corresponding to the cuneus).

In a synthetical survey on alexia, De Massary (1932) ascertained that in 'pure' word blindness the lesion prevailingly affects the gyrus lingualis and the gyrus fusiformis. Lesions of the fibres of the corpus callosum were also reported in some of the cases examined at necropsy (Foix and Hillemand, 1925; Kleist, 1934; Gloning, Gloning, Seitelberger, and Tschabitscher, 1955).

In our case there are several arguments in favour of a prevailingly left occipital location of the lesion; namely the absence of disturbances of receptive speech; an association with agnosia as regards colours; conservation of spontaneous writing and of writing to dictation, which, as pointed out by Pötzl (1927) and by Ajuriaguerra and Hécaen (1960), are always impaired in parietal alexia. The major clinical symptoms exhibited by our patient suggest a preponderance of the lesion in the peri- and left parastriate areas (areas 18 and 19 of Brodmann). In this sense, the pathological findings reported by Sittig (1921) and by Kleist (1934) are worth mentioning. In their cases of colour agnosia lesions were found in area 19 of Brodmann. Yet, the presence of constructional apraxia and of a discrete anomia points to the parietal involvement of the adjoining zone (Brodmann's areas 40 and 39). The absence of the great syndromes (receptive aphasia, agraphia) generated by lesions of these left parietal areas leads us to suppose that in our case parietal involvement was but slight, the main lesion being the left occipital one.

The comparatively sudden onset, the regressive course, the vascular antecedents suggest a vascular aetiology. The vascular lesions were confined to the posterior cerebral artery. By taking into account the limited nature of the lesion, the existence of a thrombosis of a cortical branch of the posterior cerebral artery seems most likely, perhaps thrombosis of the left lingual artery as asserted by Kroll (quoted by Leischner, 1957).

Ophthalmological findings (Dr. Florentina Lascu) in our patient showed that fixation and scanning on the median line were good. A slight fixation deficit on the hemianopsic side, as expressed by nystagmiform movements to the right, was present. The fixation deficit on the hemianopsic side was first reported by Holmes (1921) in brain injuries of the occipital lobe. He accounted for this symptom by the interruption of the corticotectal fibres as demonstrated pathologically. The fact that there were no differences between reading in the right visual field (blind) and the left visual field (unimpaired) and that right homonymous hemianopsia was compensated, the patient displaying correction movements of the head and eyeballs for right homonymous hemianopsia, has led us to attach no pathological importance to the fixation deficit in the right hemianopsic fields for alexia. In this connexion, it must be mentioned that Warrington and Zangwill (1957) attached no importance to fixation disturbances of the eyeballs, except in cases of uncompensated right homonymous hemianopsia, arguing that in this condition, too,

fixation disorders may possibly be secondary to alexia when ocular fixation is difficult owing to the patient's inability to understand the sense of the words he reads. No concentric constriction of sight was observed to exist, which might justify the assertion that there exists a functional lability of the visual system (Beringer and Stein, 1930). At the same time no disturbances of visual orientation were found to be present (Martin, 1954).

In our patient, alexia is the consequence of visual agnosia, displaying a more complex nature and comprising also agnosia for colours and for geometrical forms. It is significant that the graphic-motor picture of the written symbol of language was intact as the patient could write but could not read what he had written. He had the mental image of the graphic sign and could express it by an adequate motor action (graphically) but when seeing the graphic sign could not form the pertinent mental picture. Interior language was very well preserved. The patient was not really aphasic but agnosic for certain symbols and for colours. Only the optic symbol of the letters was altered in our patient, for the symbols conveyed by other pathways, dermolexia, feeling of letters, succeeded in releasing the mechanism enabling him to recognize the symbol preserved as such.

In our case particular importance in understanding the pathophysiological mechanism of alexia must be attached to the tests of visual and auditory unblocking. They demonstrate the possibility of reading words and even sentences with the aid of visual and auditory cues (other than those of the written symbols of speech) when direct perception or understanding of the words or sentences was impossible. These facts suggest, on the other hand, that the pictures of the symbols of language were not destroyed but merely could not be evoked visually. Reading, as emphasized by Leischner (1957), appears to be the result of an association of various functions, *i.e.*, optic, gnosic, opticokinetic, acoustic, verbal, motor, and ideatory functions. Among these functions, the optic and acoustic components are predominant. The total absence of receptive language disturbances afforded us the opportunity efficiently to use the methods of auditory unblocking whereby a high reading score was attained (80-100%) as compared with a direct reading score of 0.

Another convincing test regarding the preservation of the pictures of written language symbols is the *quasi*-normal performance of spontaneous writing and writing to dictation.

The fact that visual and auditory facilitation (unblocking) as well as other tactile, proprioceptive facilitations exert a transitory effect on lexia strictly limited to the period of their action, is in favour of the interpretation of 'pure' alexia as a disruption of the functional connexions between the various anatomical structures and pathways upon which normal reading depends.

Summary

A right-handed patient is reported, whose past history included lues and arterial hypertension, and in whom word blindness set in suddenly, associated with right homonymous hemianopsia, dysgraphia in copying, colour agnosia, constructional apraxia, slight anomia but no disturbance of receptive speech.

The use of facilitating (unblocking) auditory and visual tests made possible the reading of certain words and sentences which the patient had been unable to read when presented in isolation.

The role of the various sensory inputs in the mechanism of reading and of the sites of lesion which may evoke 'pure alexia' are discussed.

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OPHTHALMODYNAMOMETRY IN CAROTID ARTERY DISEASE

BY

R. W. ROSS RUSSELL* and W. I. CRANSTON

From the Department of the Regius Professor of Medicine, University of Oxford

It is commonly believed that disease of the carotid artery may cause cerebral symptoms, although the way in which these come about is still uncertain.

The pressure changes in the upper part of the carotid artery are thus of great interest and may be approximately followed by measuring the ophthalmic artery pressure. This report is concerned with such measurements in different kinds of carotid disorder.

Method

The Baillart ophthalmodynamometer (dial type) was used and the technique of measurement has been discussed elsewhere (Hartmann, 1949). Readings were taken to the nearest 5g. The instrument was frequently recalibrated and a correction made for the weight of the plunger. The patients sat or lay supine and the systemic blood pressure was measured by the same observer with an arm cuff just before dynamometry. Apart from subconjunctival haemorrhage (one case) and corneal abrasion (one case), there were no complications. Patients with glaucoma, severe myopia, or retinal detachment were not examined.

Results

Normal Subjects.—Ophthalmic artery pressure (OAP) and systemic blood pressure (SBP) were measured in 98 adult subjects without signs or symptoms of cerebral or ocular disease. There were 63 patients in the age group 51 to 70 (106 eyes

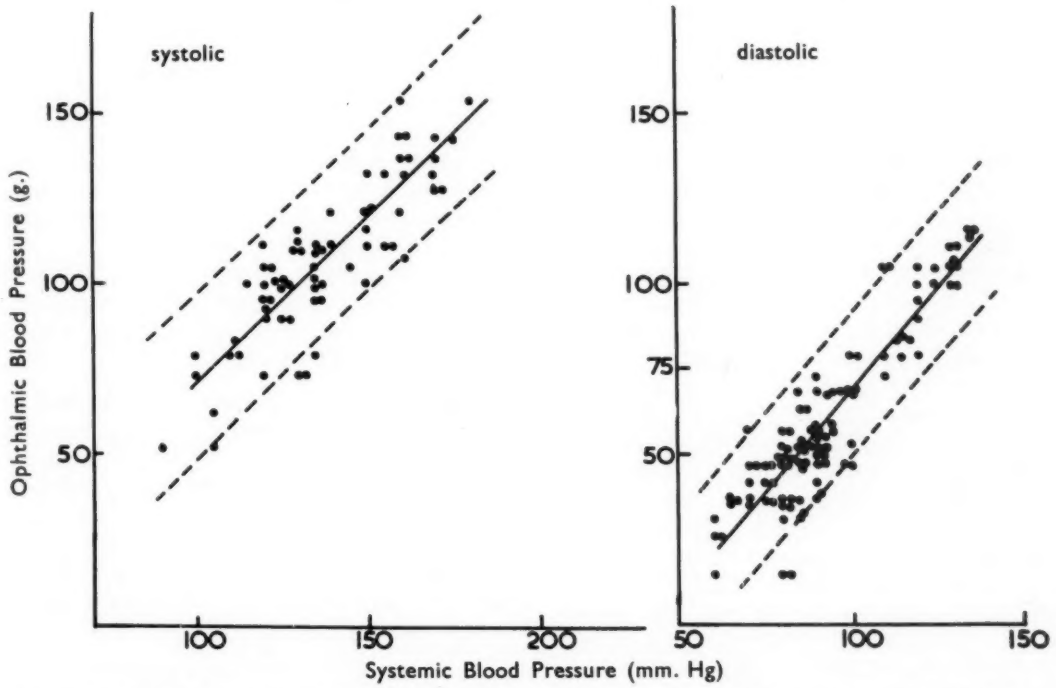

FIG. 1.—Relationship of OAP to BP in normal subjects over 50 years. The dotted lines show the 95% confidence limits.

*E. G. Fearnsides Scholar, University of Cambridge.

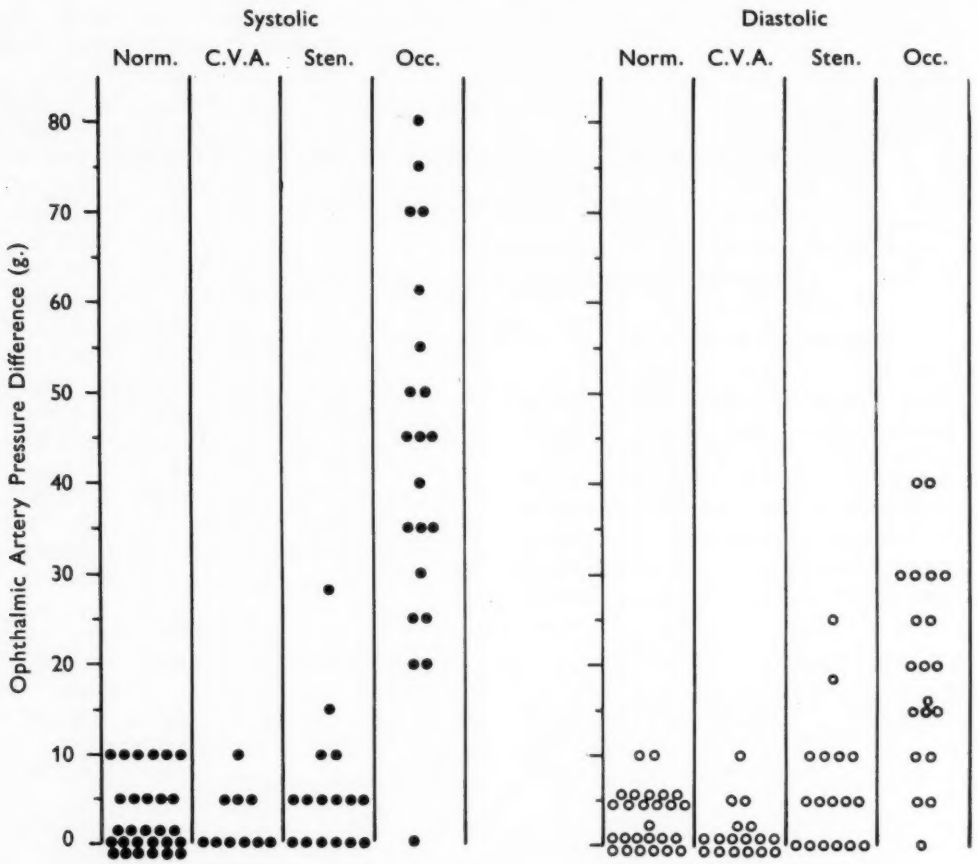

FIG. 2.—Differences in ophthalmic arterial pressure between two eyes in 28 normal patients, and in patients with cerebral vascular disease. Closed circles represent systolic levels, open circles diastolic levels.

examined) and 35 patients in the group 14 to 50 (45 eyes examined). The relationship between systemic and ophthalmic pressure in patients over 50 years of age is shown (Fig. 1) and is expressed by the equation OAP g. = (SBP mm. Hg × 0·98) −26·8 for systolic readings and OAP g. = (SBP mm. Hg × 1·18) − 49·1 for diastolic readings. The slopes of the two regression lines are significantly different (variance ratio 5·33; p = < 0·05).

When patients under 50 are considered, the same difference between systolic and diastolic readings is apparent although the total numbers are less.

OAP g. (systolic)=(SBP mm. Hg×1·00)−31·2

OAP g. (diastolic)=(SBP mm. Hg×0·83)−23·7

Variance ratio 1·25, p=>0·2.

There is an insignificant difference between the younger and the older group when systolic slopes are compared. The diastolic slopes are different but this is probably due to the inclusion in the older group of a larger number of hypertensive subjects since the slopes do not differ significantly when older patients with diastolic pressures over 100 mm. are excluded. This does not necessarily mean that the relationship OAP/SBP is different in those with hypertension but is due to the small scatter of blood pressure readings below 100 mm.

There was good agreement between the pressures measured in the two eyes of individual patients, the difference, systolic or diastolic, being never more than 10 g. (Fig. 2).

Cerebral Vascular Disease.—Ophthalmic artery pressures were measured in 15 patients recently admitted to hospital with a clinical diagnosis of cerebral thrombosis in whom angiography of the suspected carotid artery showed no abnormality. Ophthalmic artery pressures on both the sound and the suspected side differed by less than 10 g. and both were within normal limits when related to blood pressure (Fig. 3a).

Carotid Stenosis.—Seventeen patients with recent cerebral symptoms, either transient or permanent, in whom angiography showed carotid stenosis were examined in the same way. The majority of OAP

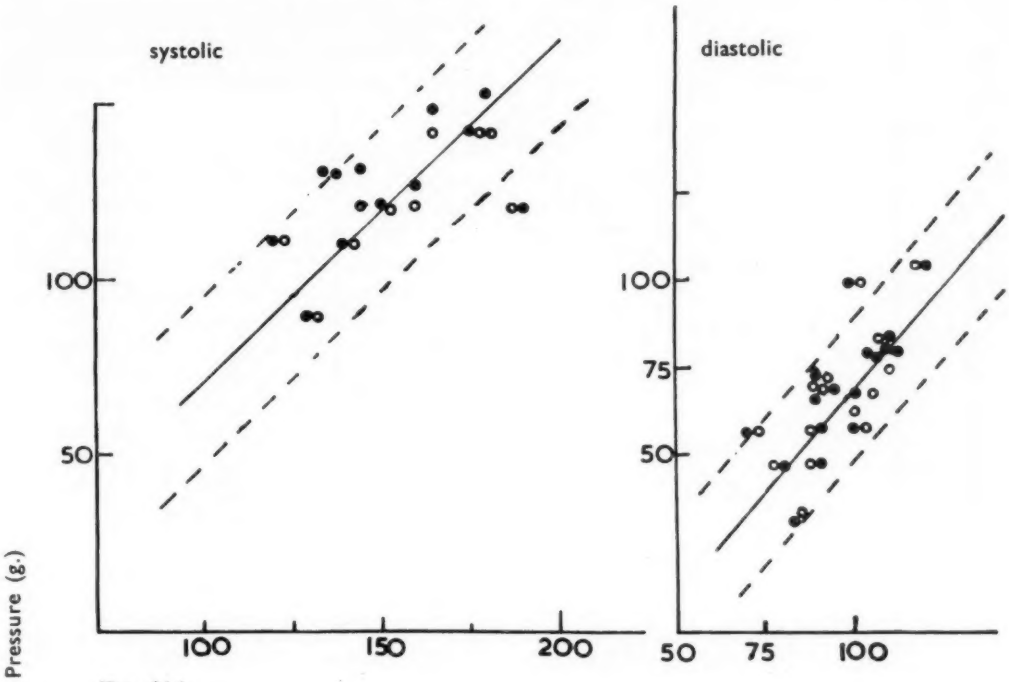

FIG. 3(a)

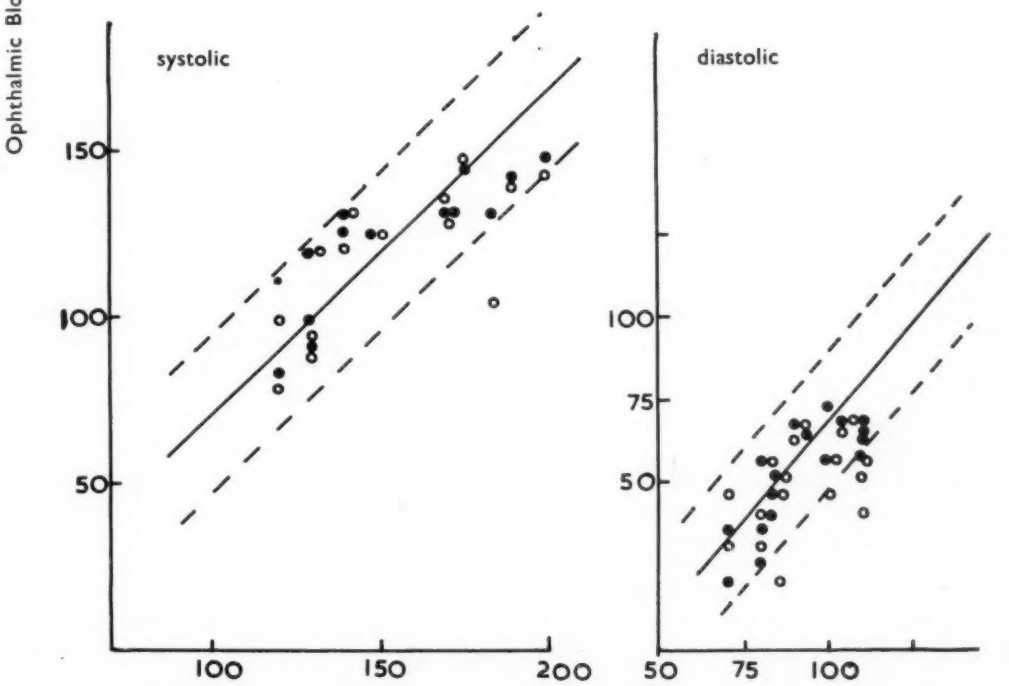

FIG. 3(b)

FIG. 3.—Relationship of OAP to BP in cerebral vascular disease (*a*) normal angiogram, (*b*) carotid stenosis, (*c*) carotid occlusion. Closed circles normal side. Open circles suspected side. Dotted lines show 95% confidence limits for normal subject over 50.

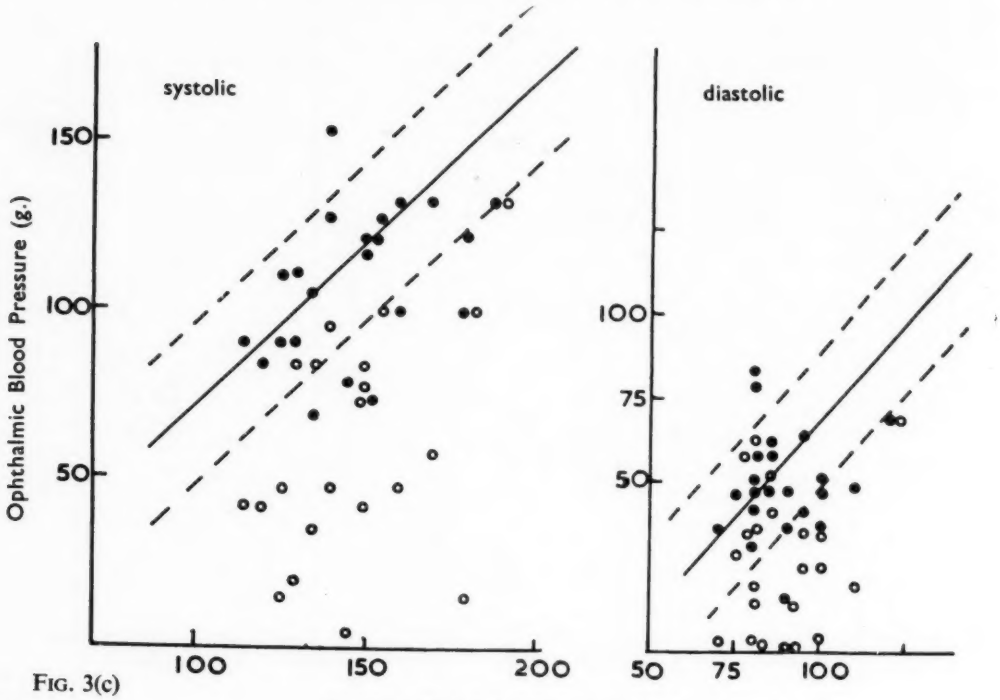

FIG. 3(c)

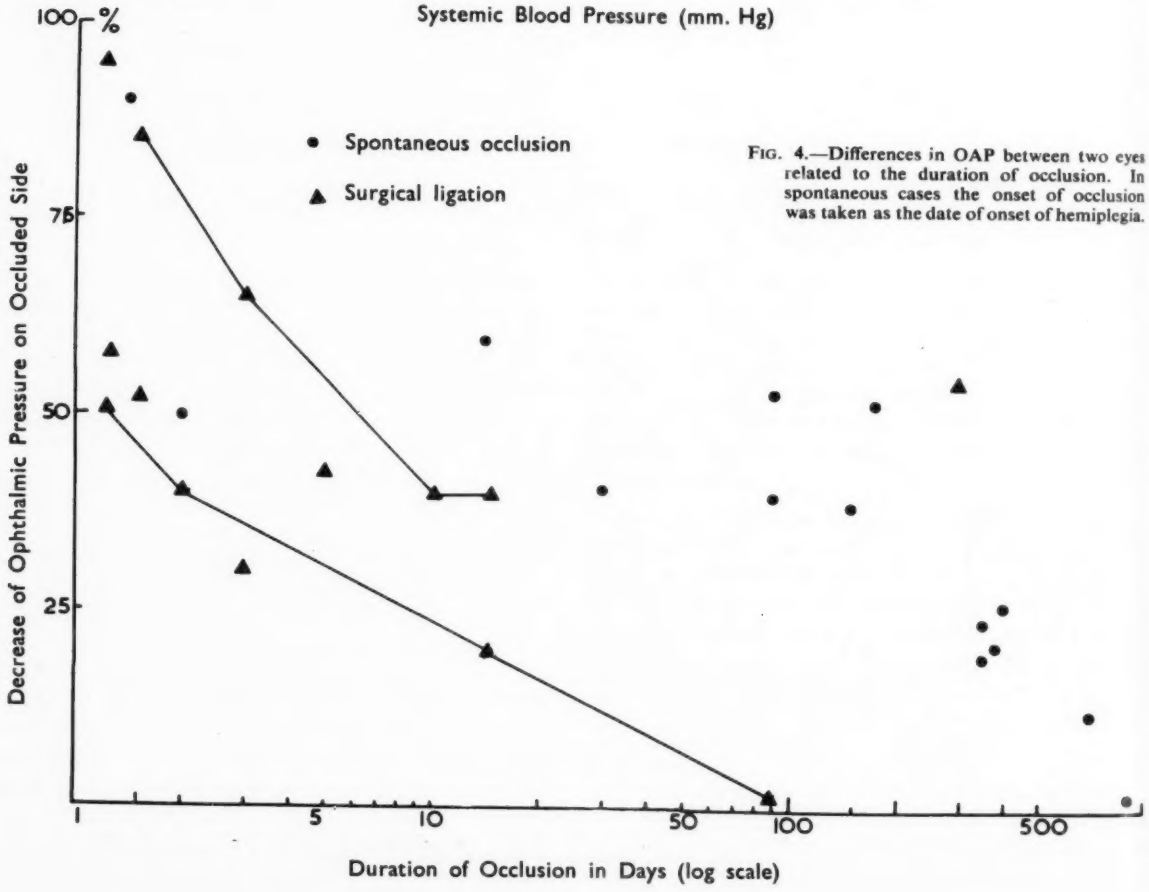

FIG. 4.—Differences in OAP between two eyes related to the duration of occlusion. In spontaneous cases the onset of occlusion was taken as the date of onset of hemiplegia.

readings were within normal limits (Fig. 3b) and the difference between the two eyes of individual patients was less than 10 g. in all but two cases (15 g. and 27 g. systolic).

Carotid Occlusion.—Twenty-one patients with complete carotid occlusion were examined. Fourteen were cases of spontaneous internal carotid occlusion mostly with recent symptoms and seven had undergone common carotid ligation for intracerebral aneurysm. Ophthalmic systolic readings were abnormal in all but two cases but about a third of diastolic readings fell within the normal range (Fig. 3c). A comparison of pressures in the two eyes in most cases showed a difference of greater than 20 g. systolic, the occluded side having the lower pressure. Diastolic differences were less marked. In general the greatest pressure differences were found in patients with very recent symptoms or immediately after carotid ligation. Longer standing cases showed less abnormality (Fig. 4) and a series of measurements on a patient after carotid ligation showed that the ophthalmic pressure returned to normal within three months, presumably as a result of increased collateral supply.

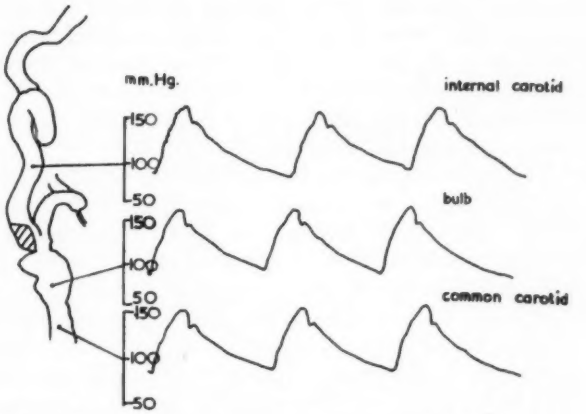

FIG. 5.—Pressure measurements taken at operation in a case of carotid stenosis. Readings were taken successively and not synchronously (Statham strain-gauge manometer).

Discussion

Ophthalmodynamometry has many limitations, since it cannot allow for variations in intraocular tension, scleral rigidity, or the elasticity of retinal arteries. The intraocular tension is raised until blood flow is arrested and at this point it equals the pressure at the first proximal branch, *i.e.*, the ophthalmic artery (Duke-Elder, 1926). Results in normal subjects show that the most important variant is systemic blood pressure and the relationship between eye and arm blood pressure are different from systolic and diastolic readings. There are several possible interpretations for this, but none is conclusive on the available evidence.

In Bailliart's hands (Bailliart, 1928) the reading for ophthalmic diastolic pressure in grams was equal to the diastolic systemic pressure in mm. Hg and this was presumably achieved by calculating the appropriate area of the foot-plate pressing on the eye. In the present series the regression line relating ophthalmic to systemic pressure had a slope which approached unity but when extrapolated did not pass through zero but intersected the abscissa at about 25 mm. The difference between these results and those of Bailliart and other workers (Bidault, 1931; Streiffe, Audéoud-Naville, and Audéoud, 1937) is probably due to minor variations in technique as in the arbitrary point taken as the diastolic level.

Previous reports on the value of ophthalmodynamometry in detecting carotid occlusion are confirmed (Thomas and Petrohelos, 1953); Wood and Toole, 1957; Heyman, Karp, and Bloor, 1957). A difference in pressure of more than 25 g. between the two eyes is almost diagnostic and a difference of this order is more likely to be found in systolic than in diastolic readings and in recent rather than late cases. The origin of the internal carotid artery may be explored on this evidence alone if angiography is not available. Conversely a small difference in ophthalmic pressure between the two sides in a proved case of complete carotid occlusion indicates that the obstruction has been present for some months and that surgery will probably be useless.

Milletti (1950) has shown that in cases of carotid occlusion where routine dynamometry shows no difference in pressure, compression of the patent carotid for 30 seconds produces a large fall in both eyes, more marked on the occluded side. This is too hazardous to become a routine procedure but compression for periods of a few seconds may be sufficient for diagnosis (Lowe and Stephens, 1961).

The normal findings in cases of carotid stenosis show that the flow through the damaged artery and through the collaterals is sufficient to maintain a normal pressure in the ophthalmic artery and probably in the upper part of the internal carotid (Duke-Elder, 1926). Direct measurement at operation confirms that in such cases there is only a slight pressure gradient across a stenosis (Fig. 5). This does not necessarily imply that blood flow through the stenosed segment is normal, since a normal pressure may be found with complete block in the presence of good collaterals.

Pressure measurements, both direct and indirect, are of interest in connexion with transient cerebral ischaemic attacks. These occur in various forms of

cerebral vascular disease but are particularly associated with carotid stenosis. They are commonly thought to be the result of a fall in systemic blood pressure which produces a temporary vascular insufficiency in the territory of a damaged artery (Meyer, Fang, and Denny-Brown, 1954).

Clinical observations have shown this mechanism to operate in some patients (Shanbrom and Levy, 1957; Eastcott, Pickering, and Rob, 1954) but in others transient attacks seem to occur without change in pulse or blood pressure (Alajouanine, Lhermitte, and Gautier, 1960). Further, while large falls in blood pressure are frequently produced by treatment in hypertensive patients, many of whom also suffer from occlusive cerebral vascular disease, it is unusual for a focal ischaemic attack to occur (Fazekas, Kleh, and Parrish, 1955). If transient attacks are due to temporary falls of pressure in the carotid territory, and if the dynamometer reflects the pressure changes in the upper part of the artery, it would be expected that patients with a recent carotid occlusion who show a marked fall in ophthalmic pressure would suffer frequently from transient attacks.

In fact transient attacks are very rare after carotid ligation and are more often associated with carotid stenosis, and since there is no reason to suppose that falls in systemic blood pressure occur more frequently in carotid stenosis than occlusion, it seems that factors other than blood pressure may be operating. The observations of Fisher (1959) on a patient during an attack of monocular blindness and the effect of anticoagulant drugs on transient cerebral ischaemia (Siekert and Millikan, 1955) have revived interest in cerebral embolism, and more evidence on this important point is needed.

Summary

Measurements of ophthalmic artery pressure and of systemic blood pressure were made in normal subjects and in patients with carotid stenosis and occlusion. A reduction in ophthalmic pressure was found in recent cases of carotid occlusion but not in carotid stenosis. The significance of these findings with regard to the symptoms of carotid disease is discussed.

I am indebted to Dr. W. Ritchie Russell, Mr. J. B. Pennybacker, and Professor Sir George Pickering for permission to report cases under their care.

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APPARATUS FOR MEASURING AND COUNTING MYELINATED NERVE FIBRES

BY

M. L. E. ESPIR* and D. T. C. HARDING

From the National Hospital for Nervous Diseases, Queen Square, and the Physics Department, King's College Hospital

In recent years the fibre spectrum of myelinated nerves showing the proportion of fibres of different diameters has attracted increasing attention. For the purposes of some research requiring such fibre analysis, we developed apparatus for measuring and counting myelinated nerve fibres and it has proved to be of great assistance in this kind of investigation.

Methods

Transverse sections of nerve are prepared using a standardized histological technique, myelin sheaths being stained black with osmic acid, and photomicrographs of these sections are enlarged so that the final magnification is 1,000 times the original size. The apparatus described below is then used to measure and count all the myelinated fibres individually on the photographs; all measurements in millimetres represent microns in view of the selected magnification of 1,000.

The Apparatus

Counters.—Fig. 1 shows the basic unit, which consists of a set of 15 electro-magnetic counters, each registering only when one particular size of fibre is measured. A sixteenth counter situated at the side of the instrument registers the total number of fibres of all sizes. An 18-way socket has been incorporated to take an appropriate plug through which all the leads from the measuring device (described later) are connected individually to the counters. Thus different types of measuring devices can be plugged in for use as required.

The electrical circuit of the counting unit, which is mains operated, is as in Fig. 2 (*i.e.*, within the dotted line). Each individual counter is operated in a simple series circuit through the contact selector which is an integral part of the measuring device. The counter for indicating the total number of fibres measured is placed in series with the counter common line and this will register each time any individual counter operates. The counters used are the miniature post office type readily obtainable from government surplus suppliers, costing approximately 12s. 6d. each. The electrical components are quite standard costing in all about £3. The total cost, including all the component parts and materials used in the instrument, amounted to approximately £15.

The instrument was built into a rexine covered case measuring 10 in. × 8½ in. × 5 in.

Measuring Devices.—Three different types are described.

Protractor Type.—Fig. 3 shows a photograph of the perspex protractor. The graduated holes for measuring the diameters of the myelin sheaths have a size range from 2 to 16 mm. Opposite each hole can be seen the brass contacts spaced in the form of an arc of smaller radius than the holes, each contact being connected back into the 18-way plug. The centres of the holes lie on an arc of 5 cm. radius, and the contact selector arm, pivoted at the centre, is rotated to overlie the hole which has the same diameter as the myelin sheath being measured. The button is then depressed, and the hardened steel pin passes through the hole in the protractor to pierce the under-

FIG. 1.—Universal counter unit showing 16 counters; the perspex protractor measuring device and the 18-way multiplug are housed in the case of the box.

*Present address: Leicester Royal Infirmary.

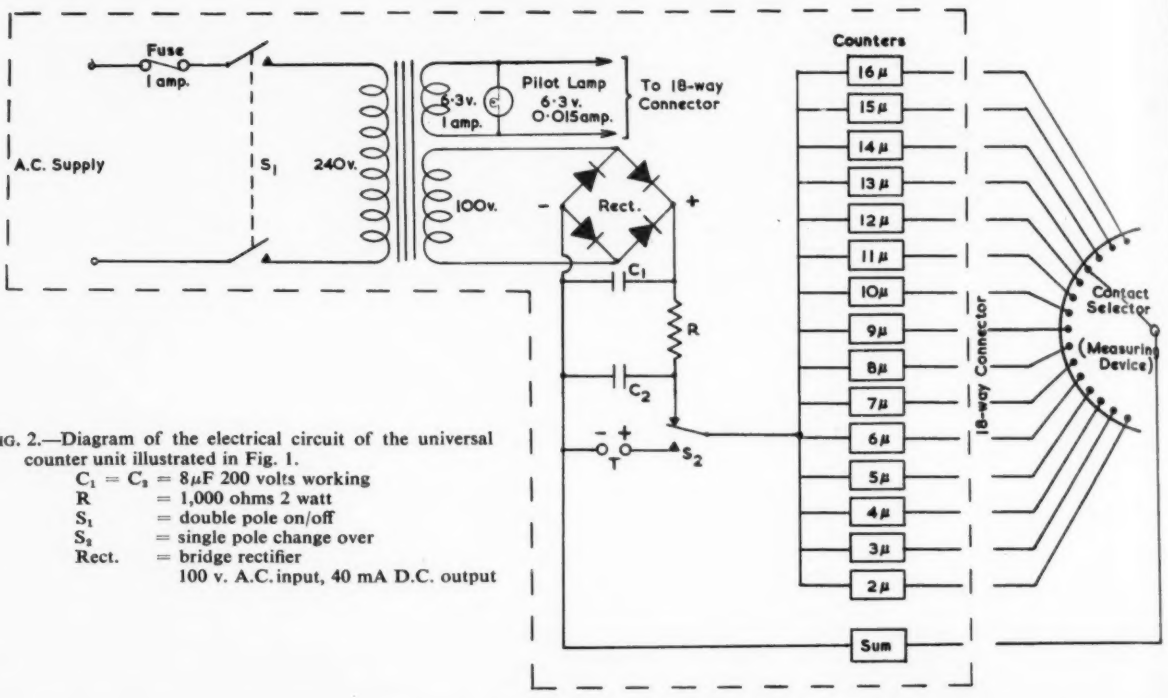

FIG. 2.—Diagram of the electrical circuit of the universal counter unit illustrated in Fig. 1.

$C_1 = C_2$ = 8μF 200 volts working
R = 1,000 ohms 2 watt
S_1 = double pole on/off
S_2 = single pole change over
Rect. = bridge rectifier
100 v. A.C. input, 40 mA D.C. output

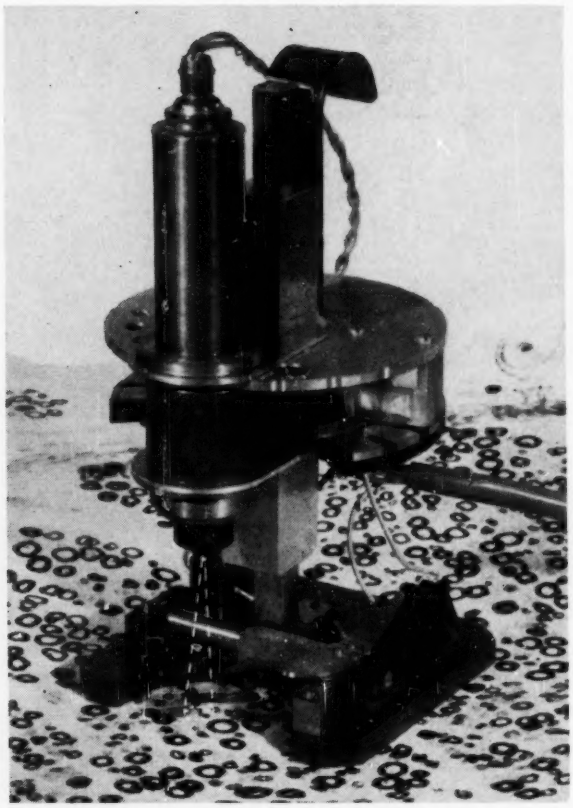

FIG. 4.—Light beam type of measuring device in use over the photomicrograph. The light beam is indicated by the dotted line.

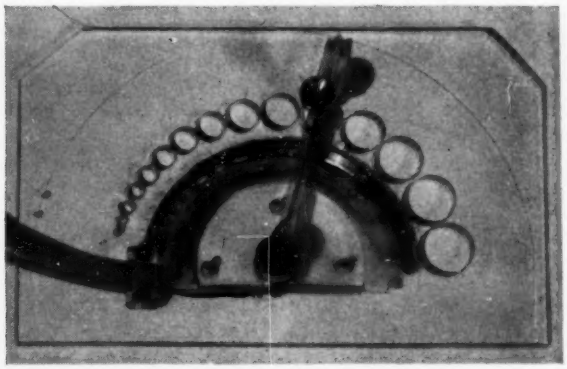

FIG. 3.—Perspex protractor type of measuring device.

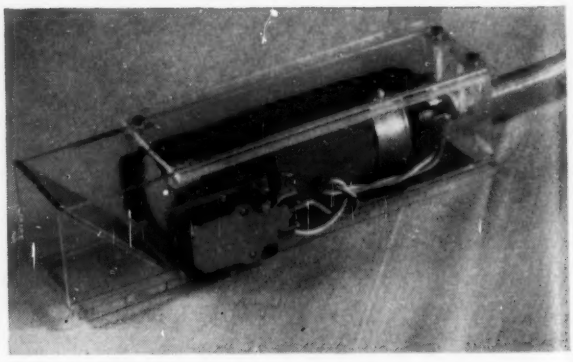

FIG. 5.—Cathode ray tube type of measuring device.

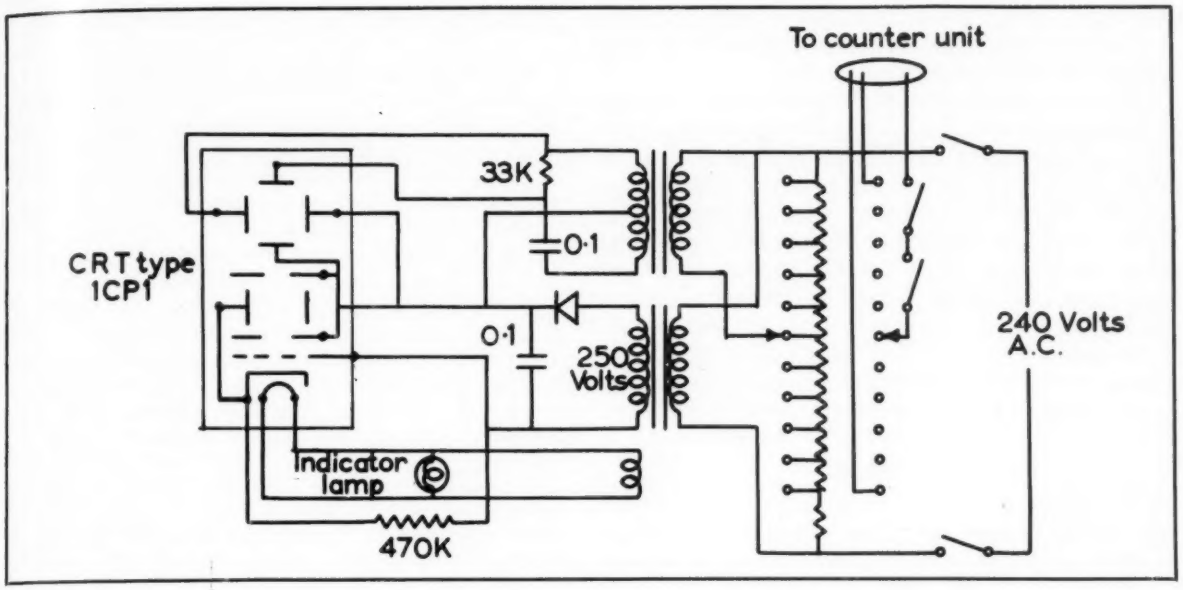

FIG. 6.—Diagram of the electric circuit of the cathode ray tube type of measuring device.

lying photograph, thus marking the centre of the nerve fibre measured. Simultaneously a metal brush on the underside of the sprung contact selector arm is made to touch the associated contact, completing the circuit back to the appropriate and 'total' counters. By releasing the button, a spring lifts the pin to its resting position, and the contact selector arm rises to its original position thus opening the electrical contact.

Light Beam Type.—A beam of light is shone from a fixed point above the photograph (Fig. 4), the 6·3 volts supply for the light source being obtained from the mains counter unit via two pins of the 18-way plug. A series of graduated holes cut in a circular metal plate can be rotated so that the beam of light is made to pass through each hole as desired. The diameter of the circle of light shining on the photograph can thus be altered from 3 to 16 mm.

The instrument is moved over the photograph so that the centre of the beam corresponds with the centre of the nerve fibre to be measured, and the metal plate is rotated until the outline of the light fits the circumference of the myelin sheath. Separate contacts made for each hole in the metal plate are individually connected to the series of counters in the box through the multiplug. When the appropriate hole in the metal plate has been selected, contact is automatically made with the counter corresponding to the size being measured. The circuit is then completed for registration on the appropriate and total counters when the microswitch is triggered by depressing the lever. At the same time as the lever is depressed, the fibre measured is worked by the overlying point.

Cathode Ray Tube Type.—The electron beam of a 1 in. cathode ray tube is made to generate a circular trace on the fluorescent screen. An image of this illuminated ring is made to appear coincident with the nerve fibre being measured by viewing both the photomicrograph and the cathode ray tube screen through a half-silvered mirror set at 45° (Fig. 5). Parallax is thus eliminated, giving less restriction on the angle of view. The diameter of the circular trace may be readily changed by adjusting the voltage applied to the deflecting circuit used, and the 11-position switch gives the range of 4 to 14 millimetres. An additional wafer on this switch selects the appropriate counter; Fig. 6 shows the electrical circuit.

In use, the diameter of the ring is matched to the myelin sheath being measured, and the perspex frame is then pressed to the paper. This causes the pin set in the base of the frame to pierce the centre of the fibre and at the same time operates the microswitch to register on the appropriate and total counters.

Comment

Using these measuring devices it is possible to analyse a nerve containing 1,000 fibres in approximately one hour, and, as with many machines, speed and accuracy can be increased with practice. In order to avoid the possible error of counting the same fibre more than once, each device is so constructed that a marker is linked with the switch which operates the counters, so that each fibre is clearly marked on the photograph at the same time as it is measured and counted. The resulting histogram is of interest for the study of peripheral nerves in health and disease, and a report of some of the findings will be published later.

Types 2 and 3 have the additional advantage that the beam or ring of light only has to be centred once over the fibre being measured, and can then

be taken through the size range in the same position, *i.e.*, without having to re-centre for each size being tested, as with the protractor type.

It is fully realized that there is still room for further improvement in the design of devices of this kind, and different methods of measuring other than the three described may be used. It is also possible that similar devices may have an application for other work involving counting and measuring, in which case the number (and shape) of gradations with corresponding counters may be altered according to the range required and purpose of the analysis. The multiplug is therefore invaluable because different measuring devices can be connected for use with the same box of counters.

Summary

A universal counter unit and three different measuring devices have been described as having special advantages for the analysis of myelinated fibres from photomicrographs of nerve sections.

We should like to thank Dr. E. S. Schuster, O.B.E. (Oxford) and Mr. H. B. Morton (Department of Applied Electrophysiology, National Hospital, Queen Square), for the measuring devices Types 2 and 3 respectively, and for their help in the preparation of this paper. We are also grateful to the principal physicist, King's College Hospital, for facilities and advice. Photographs of the devices were taken in the Photographic Departments at the National and King's College Hospitals.

M. L. E. E. wishes to acknowledge with thanks the facilities and financial help made available by Mr. Harold Edwards, Director of the Department of Surgery, King's College Hospital Medical School, the work of his technician, Mr. Colin Urwin, who prepared the histological section and photograph of the nerve shown, and a research grant (which has covered some of the cost of materials) from the Institute of Neurology, The National Hospital for Nervous Disease, Queen Square, where this work was started as clinical assistant to Dr. R. W. Gilliatt.

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SUPPURATIVE LESIONS OF THE BRAIN-STEM

BY

ALLAN HULME

From the South-Western Regional Neurosurgical Unit, Frenchay Hospital, Bristol

In contrast to the frequency with which abscesses occur elsewhere in the brain, suppuration confined to, or extending into, the brain-stem is rare.

Cassirer (1902) reported one case of pontine abscess and abstracted 10 from the literature. Further cases were added by Bregman (1906), Lichtenstein and Zeitlin (1936), Gaida (1939), and Roger, Poursines, Roger, and Tamalet (1951). Richland (1952) traced 15 cases in the literature and added a further one; of these, five were attributed to direct spread of infection from the ear, while the remainder were of metastatic origin. A further instance was reported by Sutin (1958).

Weickhardt and Watts (1944), describing a case of abscess in the medulla oblongata, found nine previously recorded instances, of which only three, those of Schlesinger (1894), Moniz (1934), and Norman (1941), were confined to the medulla. In their own and other cases the lesion extended into the pons or upper cervical spinal cord. Six cases were derived from distant foci and two from the ear. The origin of the remainder was obscure, though one, that of Abercrombie (1836), is thought to have been a tuberculoma.

As would be expected, the neurological manifestations vary widely, and change with progression of the pathological process, according to the cranial nerve nuclei and fibre tracts involved. Commonly, fairly accurate anatomical localization is possible.

In all reported cases, the condition has progressed, usually in a matter of days or weeks to a fatal termination. Scalabrino and Clivio (1951) reported recovery following systemic and intrathecal penicillin therapy in a case of presumed metastatic suppurative inflammation in the midbrain. The diagnosis, however, appears not to have been established with certainty. The following cases illustrate the difficulties encountered in diagnosing this condition, even with the aid of contrast radiography.

Case Reports

Case 1.—N.D.P., a 40-year-old woman, presented with an 11-day history of anorexia, and one week's history of increasingly severe frontal headache accompanied by vomiting, pyrexia, and drowsiness. Three days after the onset of headache, slurring of speech and weakness of the right upper limb were noted.

On admission she was dehydrated, febrile (temperature 101·2°F.), and restless. She was unable to speak, and the right limbs were paralysed and flaccid. No facial paresis was noted. The ocular fundi showed bilateral early papilloedema, and she was thought to have a right homonymous hemianopia.

There was moderate neck rigidity. The findings indicated a lesion of the left cerebral hemisphere but carotid angiography showed no displacement of vessels or other abnormality.

Cerebrospinal fluid examination performed on seven occasions revealed a moderate pleocytosis, varying between 86 and 350 leucocytes per c.mm., with a preponderance of lymphocytes. Protein ranged between 60 and 228 mg. per 100 ml.; 20,000 units of penicillin were instilled intrathecally on four occasions. After transient improvement her condition deteriorated further, with deepening coma and development of a right oculomotor palsy and right facial paresis. Ventriculography showed mild ventricular dilatation; the third and fourth ventricles and aqueduct were normally situated, but air failed to emerge from the fourth ventricle into the basal cisterns, suggesting obstruction due to inflammatory adhesions in the region of the foramen of Magendie. Continuous ventricular drainage was instituted. Further progression of neurological dysfunction, including paresis of the left lower limb and a left external rectus palsy preceded death, 17 days after the onset of her illness.

At necropsy, the principal pathological findings outside the cranial cavity were acute cholecystitis and bilateral patchy bronchopneumonia.

The cerebral hemispheres and cerebellum appeared normal on inspection but the pons had a greyish pink appearance and was extensively softened. Serial sections of the hardened brain showed discoloration and softening, mainly in the right side of the pons, extending into the midbrain as far as the substantia nigra, across the midline and downwards to the upper end of the medulla. A few areas of yellow pus were seen in the softened area. Histological examination showed suppurative encephalitis with multiple early abscess formation.

Case 2.—Mrs. V.K., aged 43 years, gave a history of recent exacerbation of bronchitis, with mucopurulent sputum. Over a period of three days she had developed numbness and weakness of the left limbs, starting with

tingling in the hand, and accompanied by occipital and post-nuchal headache. During the same period she had noted diplopia, slurring of speech, and difficulty in breathing.

On admission she was obviously ill, and there were signs of bronchopneumonia. Neurological examination revealed paresis of the right external rectus muscle, impaired palatal movement, and deviation of the tongue to the right on protrusion. The left limbs were paretic and the left plantar response extensor.

The cerebrospinal fluid was under a pressure of 140 mm., and contained 2 white cells per c.mm., protein 85 mg. per 100 ml., with increased globulin, and sugar 52 mg. per 100 ml.

Two days later, she showed impairment of all conjugate eye movements, particularly to the right, and slight skew deviation of the eyes, the left being a little up and the right a little down. The right pupil was a little larger than the left, but both reacted to light. Hypalgesia of the left limbs, trunk, and face was noted and right corneal sensation also seemed to be diminished. In addition to the paresis of the left limbs, there was a well-marked right facial weakness of lower motor neurone type. She was markedly deaf in the right ear, but there were no signs of aural infection.

The clinical signs suggested a progressive lesion in the brain-stem and contrast air studies were advised. No air entered the ventricles on attempted lumbar air encephalography, but subsequent ventriculograms appeared normal; in particular there was no apparent distortion or obstruction of the third or fourth ventricles.

A second cerebrospinal fluid examination revealed 65 white cells per c.mm. (16% polymorphonuclear leucocytes and 84% lymphocytes); protein 50 mg. per 100 ml. and sugar 97 mg. per 100 ml.

Electroencephalography gave a record barely outside the normal range of variation and with no localizing features.

Culture of the sputum yielded a pneumococcus which was sensitive to tetracycline and treatment with the appropriate antibiotic was given. Anticoagulants were administered on the assumption that the cerebral lesion was a vascular thrombosis. Her condition deteriorated, however, and she died 16 days after admission to hospital.

At necropsy a solitary abscess containing thick green pus was found in the right half of the pons. It measured 1·5 cm. from above down, 2·2 cm., antero-posteriorly, and 1·8 cm. transversely. It bulged into the floor of the fourth ventricle but had not ruptured (Fig. 1).

Case 3.—Mrs. A.M., aged 41 years, had suffered from migrainous attacks for many years. Four days before admission she awoke with frontal headache and seemed dazed and clumsy in her movements. She appeared to see more clearly with one eye closed, possibly due to diplopia. Some hours later she suddenly became unconscious and on admission to hospital she was comatose with dilated non-reacting pupils, spasticity of all limbs, and periodic respiration. During the next four days her condition remained essentially unchanged, though the level of consciousness improved slightly, respiratory

FIG. 1.—Transverse section of pons in Case 2 showing abscess cavity.

rhythm returned to normal, and the limbs became flaccid. The plantar responses remained extensor.

Blood examination revealed moderate anaemia (Hb 57%) and 28,200 white cells per c.mm. (90% polymorphonuclear leucocytes). Bilateral carotid and vertebral angiograms provided no evidence of a space-occupying lesion or of arterial occulsion. The electroencephalogram showed delta activity from all areas of the brain with frequent monophasic complexes. The cerebrospinal fluid was normal in all respects.

A tentative diagnosis of brain-stem thrombosis was made. A blood transfusion was given to combat anaemia, the haemoglobin level having fallen as low as 42%. The patient was transferred to another hospital where she died two weeks later. Necropsy revealed bilateral bronchiectasis and a chronic multilocular abscess in the left lung.

Examination of the fresh brain suggested that there were two metastatic abscesses, one presenting on the upper surface of the right cerebral hemisphere at the junction of its anterior two-thirds and posterior one-third, and a second on the right side of the midbrain. Serial sections of the hardened brain showed that in fact there was one large communicating cavity. The right cerebral peduncle was largely destroyed. A coagulase-positive *Staphylococcus aureus* was isolated from the abscess cavity. A similar organism had been obtained from the sputum during life.

Comment

In all three cases the abscess was of metastatic origin and probably derived from the lungs. The syndrome was of sudden or rapid onset, suggesting an embolic phenomenon and the clinical pattern changed rapidly as the lesion developed.

In Cases 2 and 3, the neurological signs localized the pathological process to the brain-stem, but in Case 1 the initial syndrome of right hemiplegia, aphasia, and probable right hemianopia implicated

the left cerebral hemisphere; only later did contralateral signs suggest pathology at a lower level. A possible explanation might be that an early metastatic lesion in the left cerebral hemisphere was quelled with antibiotics and that a further embolus occurred later in the brain-stem. It is noteworthy that the inflammatory process here was at an early stage; the multiple foci of suppuration had not localized into a single cavity nor had encapsulation occurred. In Case 3 the early and rapid onset of coma and pupillary dilatation suggests involvement of the midbrain, and it seems likely that there were embolic foci here and in the right cerebral hemisphere which later coalesced to form a single cavity.

In no case was assistance in localization obtained from contrast radiography.

In Case 2 it is surprising that no distortion of the fourth ventricle shadow was apparent, despite the protrusion into the floor caused by the underlying mass (Fig. 1). It is possible that ventriculography using an opaque medium, such as Myodil, would have given more precise definition and perhaps demonstrated a deformity.

Only in Case 1 did the cerebrospinal fluid show an early pleocytosis, suggestive of a meningeal reaction.

Electroencephalography also proved unhelpful in localization.

Various authors stress the fact that embolic phenomena occur much more commonly in the distribution of the middle cerebral than of other intracranial arteries (Richland, 1952; Stuart, O'Brien, and McNally, 1955). It is presumably the relative invulnerability of the vertebral basilar system which accounts for the rarity of metastatic suppuration in the brain-stem.

Gowers (1893) found only three instances of pontine and one of medullary localization among 231 brain abscesses, and Le Fort and Lehman, quoted by Cassirer (1902), six in a series of 458.

The three cases described above occurred in a series of 105 instances of intracranial abscess during a period of 11 years. The incidence thus appears to be less than 3%.

Hitherto the diagnosis has been made only at necropsy; it seems unlikely, however, that any effective surgical intervention would be practicable even if the condition were recognized during life and its rarity is indeed fortunate.

Summary

Three cases of suppuration in the brain-stem are described and the literature briefly reviewed.

The condition is rare and the diagnosis difficult, since special radiological techniques appear to give little assistance.

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THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS: 63rd MEETING

The 63rd meeting of the Society was held on May 12 and 13, 1961, at the Rigshospitalet, Copenhagen, Denmark. The President, Mr. D. W. C. Northfield, was in the chair.

The Incidence of Cerebral Ischaemia in Spontaneous Subarachnoid Haemorrhage

R. CAMPBELL CONNOLLY (London) said that as infarction of the brain had been reported in a high proportion of cases coming to necropsy after spontaneous subarachnoid haemorrhage, and as marked narrowing of the main brain arteries was commonly seen on angiography during the first three weeks following such haemorrhage, he had made an attempt to discover how frequently severe clinical signs were due to ischaemia.

In a consecutive and personal series of 136 patients, 73 (54%) had at some time during the acute phase of their illness and before operation developed well-marked evidence of a focal lesion of the brain as shown by dysphasia, visual field defects, hemiparesis or akinetic mutism. Thirty of these patients proved to have sizeable intracerebral haematomas but in the remaining 43 no evidence of a haematoma was discovered and the signs were considered to be due to ischaemia.

It was assumed that the arterial narrowing, almost certainly due to spasm, occurred acutely at the time of a haemorrhage. It might be partly responsible for stopping the haemorrhage, but it had less desirable effects and, by suddenly reducing blood flow to the brain, might be the cause of loss of consciousness in some cases when bleeding was confined to the subarachnoid space. Afterwards it remained a potent factor in increasing morbidity and mortality. This was demonstrated by a striking difference in the mortality rates in the three clinical groups of patients. In the whole series of 136 patients there were 24 deaths (18%); of the 43 patients with focal ischaemic lesions of the brain, 18 died (43%); of the 30 with haematomas, five died (17%); while of the 63 remaining cases only one died (1·6%) from uraemia due to polycystic disease of the kidneys. The overall mortality rate after operation designed to prevent further haemorrhage was 8·3% in 60 cases.

It was concluded that ischaemia of the brain played a vital role during the acute phase following spontaneous subarachnoid haemorrhage and might constitute a hazard perhaps as great as the risk of recurrent haemorrhage. Efforts should, therefore, be made at every stage before, during, and after operation to combat the complication.

Cerebral Apoplexy: Surgical Treatment of Intracranial Haematomas

J. RIISHEDE (Copenhagen) said that in Denmark the annual number of apoplectic seizures was estimated at a minimum of 30,000. Deaths from cerebral apoplexy amounted to 100-125 per 100,000 individuals, *i.e.*, 5-6,000 each year, of whom 25% were under 65 years of age. In a consecutive series of 300 patients admitted to a neurosurgical department for cerebral apoplexy the frequency of intracerebral haematomas was 25%.

Seventy-four of 98 patients with cerebral apoplexy due to intracerebral haematomas were operated on. Forty-five were alive six months after operation and 26 of these had normal or slightly reduced working capacity at the follow-up from one to 10 years after operation.

Cerebral Apoplexy: Role of Carotid Occlusion in the Neck

C. F. BISGAARD and H. BUSCH (Copenhagen) described a series of 29 cases all of which showed stenosis or occlusion of the carotid arteries under arteriography. Nineteen were operated on and 10 treated conservatively. All patients had anticoagulation therapy. Heparin was given as an intravenous drip in acute cases. Secondary haemorrhage occurred in two cases in which intermittent heparin was used. A shunt was best established by use of a stiff, looped, large-diameter polythene tube placed in both ends of the arterial incision. This permitted increased working space and a reduction of the clamping time to four or five minutes. The shunt was most important when dealing with a stenosis, but they established it if they obtained a back-flow from a total occlusion.

Grafts were not used but in some cases the distal part of the incision was sutured transversely. Two cases not included in the series were presented, one a case of traumatic thrombus, and one with a kink of the internal carotid artery. Their results were not good but were not more discouraging than those obtained with conservative therapy. However, they still preferred to operate, especially on those patients with stenosis, because they felt it was better to discharge a patient with two functioning carotids.

They concluded that if operation for patients with occlusion were to be performed, then it should be immediate. In less acute cases of stenosis they preferred to start anticoagulation therapy before operation.

Cerebral Embolectomy

R. MALMROS (Aarhus) reported on a series of four cases operated on for occlusion of the middle cerebral artery since 1956. Three were due to emboli and one to thrombosis.

In two cases the emboli were removed through an incision in the middle cerebral artery and the arterial wall resutured. There was immediate filling of peripheral branches but no clinical improvement. The patients died six days and six weeks after operation. In the one thrombotic case the patient died on the table.

The fourth case was a woman of 29 with mitral stenosis. Embolism occurred six hours before operation. She had severe neurological signs corresponding to occlusion of the middle cerebral artery with conjugate deviation of the eyes, homonymous hemianopia, severe hemiplegia, hemianaesthesia, and absent stereognostic and position sense. The embolus occupied 10 mm. length of the middle cerebral artery but arteriography showed fairly good peripheral collateral circulation. At operation a temporary clip was placed on the internal carotid artery and the embolus removed through the anterior cerebral artery after this had been divided a few millimetres from the internal carotid artery. There was good back flow and clips were placed on the stumps of the anterior cerebral artery and the clip removed from the internal carotid. Post-operative angiography showed good filling of all the middle cerebral branches. Angiography 18 days after operation showed slight spasm in the internal carotid and the posterior cerebral arteries. She recovered slowly after the operation but two and a half months later there were no abnormal signs and mentally there was only slight euphoria, fatuity, and impairment of memory.

He concluded that it might be difficult to remove an embolus through an incision in the middle cerebral artery but that it could be removed through the anterior cerebral when it was possible to divide this without serious consequences. The results might be good even when several hours had elapsed since the embolism.

Continuous Recording of Ventricular Pressures in Neurosurgical Practice

NILS LUNDBERG (Lund) reported on a method for the continuous recording of ventricular fluid pressure. Its applicability as a routine aid in the treatment of intracranial lesions and intracranial hypertension of other origin was evaluated on the basis of his experience in 130 cases. In 51, recordings were continued for more than a week and in 17 for more than three weeks. The material was studied with respect to infection, tissue reaction, and intracranial haemorrhage. There was no evidence that the ventricular puncture or the indwelling catheter were responsible for any significant complications.

In cases of intracranial hypertension records showed a great variety of spontaneous fluctuations amongst which three main types could be distinguished. (1) Rhythmic oscillations of $\frac{1}{2}$ to 2 per minute and amplitude between 10 and 30 mm. Hg. These were found to be related to periodic breathing of the Cheyne-Stokes type and synchronous variations of the alveolar CO_2 content. (2) Waves with frequency of 4 to 8 per minute and amplitude less than 20 mm. Hg were related to similar fluctuations in systemic blood pressure. (3) Plateau waves occurring at irregular intervals with amplitude of 50 to 100 mm. Hg and lasting a few minutes up to hours were also noted. These were associated with headaches, impairment of consciousness, nausea and vomiting, flushing of the face, and motor phenomena such as rigidity and clonic movements of the limbs. These attacks were similar to those described previously as cerebellar or tonic fits, diencephalic fits, etc. It was stressed that these waves might be premonitory signs of hypertensive episodes after pneumography or acute swelling of the brain during operation and might be followed by signs of irreversible brain damage. Intermittent obstruction of the cerebrospinal fluid did not appear to be necessary to produce these waves and they were seen in diffuse tumour infiltrations with large ventricles and free subarachnoid spaces. E.E.G. recording during these waves showed no epileptic activity.

Plateau waves were only seen in association with a raised mean ventricular pressure, disappeared after temporal decompression, and could be induced by raising the ventricular pressure. He considered that they were manifestations of a critical instability of the mechanism controlling the reciprocal relationship between cerebral blood flow and intracranial pressure.

He concluded that continuous graphic recording of ventricular pressure could yield valuable information in the treatment of patients and offered the possibility of recording ventricular pressures for long periods without undue risk. Its practical value was increased by the fact that it included a rational and relatively safe procedure for ventricular drainage and pneumography.

Observations on the Use of a Cytotoxic Agent in the Treatment of Malignant Brain Tumours

W. ATKINSON (London) said that certain pharmaceutical manufacturers had begun trials with cytotoxic agents for the treatment of malignant tumours. The team at the Imperial Chemical Industries' pharmaceutical division had selected an epoxide, 32865, after animal trials, for use in man. The author confirmed their findings as to toxicity in monkeys.

Three patients suffering from cerebral gliomata were given different courses of injections of the compound into the common carotid artery after ligation of the external branch. The first two patients died but the third continued to live a somewhat sheltered life after seven months' treatment.

Details of histology, arteriographic pattern, and haematology were discussed. The outcome of the use of the compound in cases with intracranial sarcoma was mentioned. The dangers and discomfort attendant on this form of treatment and the need for careful selection of patients and regular control of blood cell levels were emphasized.

The Place of Decompression of the Posterior Root in the Treatment of Trigeminal Neuralgia

P. TAARNHØJ (Copenhagen) discussed the present position of decompression of the posterior root for trigeminal neuralgia which he had introduced 10 years ago. He stated that the procedure could be carried out by the temporal intradural or extradural route or by a posterior fossa approach. It was important to manipulate the posterior root and in his series this had been done by

running a nerve hook along the root. The importance of this manipulation had first been pointed out by Sheldon.

His series consisted of 155 patients of whom four had been treated bilaterally. The mortality had been 0·5% and the complications equally low. Patients had been followed up for as long as 10 years with an average of 6·5 years. Three patients had no relief; in one this was due to technical difficulties. Ninety patients (60%) had now had no complaints. Fifty-four (35%) had had a recurrence of pain and five had uncharacteristic sensations in the face. Almost half of the recurrences took place during the first year following surgery and 80% in the first three years. Following recurrence 21 patients had section of the posterior root and of these 37% were pain-free and in 23% pain had recurred. Fourteen patients had a second decompression and half of these were pain-free, the other half having had a second recurrence. He felt that following recurrence a second decompression produced better results than root section.

He pointed out that other workers had not had as good results, their recurrence rate in several series varying from none to 75%. He felt that some of the bad results might have been due to not manipulating the nerve at the time of operation.

He then reviewed reports of follow-up studies after various other procedures such as alcohol injection and posterior root section and noted that there were very few of these reports available. He concluded that the results of root section or alcohol injection were not as good as many people imagined and that the conservative procedure called decompression or compression should be considered when a patient with trigeminal neuralgia asked for relief.

Osteo-arthritis of the Mandibular Joint and Facial Pain

P. RASMUSSEN (Aarhus) presented material consisting of 146 patients with facial pain admitted to the State Department of Neurosurgery in Aarhus during a period of four years. Of these patients, 60 had trigeminal neuralgia, 69 atypical neuralgia, and 17 atypical facial pain.

He said that trigeminal neuralgia and osteo-arthritis of the mandibular joint had the following things in common: age distribution, sex distribution, seasonal variation and influence of the temperature, attacks of pain precipitated by functional activity, pain at first movements, and the effects of osteo-arthritic treatment.

By the objective as well as by the radiographic examination the patients with facial pain more frequently presented symptoms of osteo-arthritis than those without facial pain. Most of the patients had arthritic changes in the same side as the facial pain.

All the 146 patients were treated with intra-articular injections with hydrocortisone. In 64% they had an immediate effect. One half of the recurrences set in during the first three months. Six months after treatment, 25% of the entire series and 38% of the group with immediate effect were without pain. One year after, the numbers were 19% of the entire series and 30% of the group with immediate effect. The patients with trigeminal neuralgia had the best effect. Patients with positive and negative findings of osteo-arthritis had the same effect.

Hydrocortisone was used as a 'test treatment'. Further examinations would be necessary to judge of the importance of these results.

Extradural Haematoma at the Vertex

Presented by G. ALEXANDER (Bristol).

Occult Forms of Spinal Dysraphism

L. P. LASSMAN and MICHAEL JAMES (Newcastle) discussed their experience with certain forms of congenital spinal lesions. They considered that the original term, myelodysplasia, covered too many conditions and was no longer specific; most of them could be grouped under the heading of spinal dysraphism which indicated their common origin from failure of the embryo to develop completely in the median dorsal region. This term, therefore, included all forms of spina bifida and each case would be found to be a variation in degree of abnormality from the open myelocele at one extreme to the smallest failure of fusion of the spinous process at the first sacral vertebra at the other.

Spina bifida was common and it had been shown that certain progressive foot deformities in children, associated with this anomaly, were due to congenital lesions of the cord or cauda equina and it had been possible to make an early diagnosis in these cases. The symptoms and signs conformed to a pattern which allowed the formulation of a syndrome with characteristic myelographic findings. The most important finding on myelography was the level of the conus medullaris, and where the conus was abnormally low a lesion had always been found. At present they held the view that there would not be a surgically treatable congenital malformation of the spinal cord or cauda equina without a laminal defect.

Thirty cases had been submitted to operation. Twenty-four had presented as an orthopaedic syndrome, 13 with external manifestations. Three had presented as an external manifestation and three as a neurological bladder. Laminectomy confirmed the diagnosis and revealed lesions that could be shown to act in the following ways: Two cases had pressure bands, 15 cases had traction bands, with associated intrathecal lipomata in five cases. Combined traction and pressure bands were found in one case and diastomatomyelia in 10 cases. (This abnormality was present in 12 cases.) No abnormality was found in two. The lesions were found to be amenable to surgical treatment and, although the intention had been to prevent further deterioration, there had been noticeable improvement in two-thirds of the cases.

The Neurological Aspects of Retroperitoneal Malignancy

A. HULME (Bristol) said that infiltrating tumours in the retroperitoneal tissues might produce a syndrome closely resembling a primary intraspinal lesion such as cauda equina tumour or prolapsed intervertebral disc. An increase in the cerebrospinal fluid protein level might be found even when the spinal canal and vertebra were not directly involved.

Three illustrative case histories were presented. In two, dubiously abnormal myelographic appearances prompted a laminectomy, with negative findings.

Although the possibility of retroperitoneal disease was

suspected in each instance, this was not clinically detectable when the patients were first seen.

The finding of an abdominal or pelvic mass was delayed in the first case for two and a half months, and in the second and third for nine months. One patient proved to be suffering from an ovarian carcinoma and one from a fibrosarcoma. The third case was diagnosed clinically as a neurofibrosarcoma but this was not confirmed histologically. An interesting feature was the increase in C.S.F. protein level in the absence of a spinal subarachnoid block or direct involvement of the vertebral canal. Suggested explanations were that this was attributable to an aseptic inflammatory response in the involved nerve roots, or perhaps to interference with venous drainage from the epidural space.

The Early Diagnosis of Acoustic Neuromas

WYLIE MCKISSOCK (London) said the high mortality rate associated with total excision of acoustic neuromas was largely due to late diagnosis. With early diagnosis the mortality rate should be almost zero. During the period 1940-60 he had operated upon 270 acoustic neuromas but in only eight of these patients was the tumour less than 3 cm. in diameter. With these small tumours the operation was one of no greater difficulty than section of the eighth or ninth nerves.

Of the eight patients, five were men and three women and all complained of progressive deafness. Six complained of attacks of vertigo and six of tinnitus. Only two had noted disturbance of sensation in the face and one patient had noticed twitching of one side of the face during a two-week period.

Neurological signs were limited to the cranial nerves, all patients having some degree of deafness, six some disturbance in function of the fifth nerve but only a partial seventh nerve palsy.

Radiographs of the skull showed an enlarged porus in only two cases. In five patients the cerebrospinal fluid was examined, the protein being normal in three and 65 and 110 mg. respectively in the other two.

Air studies were performed in every case, found negative in seven but outlining the tumour in the remaining case.

Special otological testing by Dr. C. S. Hallpike or Mr. Terence Cawthorne indicated the presence of the tumour and on this evidence and clinical suspicion operation was undertaken. Once the exposure was made the tumour could be separated from the eighth nerve with a blunt hook and removed.

There was no fatality and recovery was rapid in all cases. In five cases eighth nerve function was retained, three having no increase in the pre-operative degree of deafness. In the remaining three patients hearing was lost although the nerve was macroscopically intact. Several patients showed a transient seventh nerve weakness but all recovered in a few weeks or months.

He concluded that the greatest publicity should be given in medical, neurological, and otological circles to the need for early diagnosis of these lesions by special otological tests: only in this way would the mortality from operation be reduced to a negligible level.

Experience with the Sptiz-Holter Valve in the Treatment of Hydrocephalus

V. KNUDSEN and P. HEDEGAARD (Copenhagen) reported 46 cases having ventriculovenous shunts. Seventeen cases were of communicating hydrocephalus, 18 were of obstructive hydrocephalus (10 with aquaduct stenosis, eight with tumours), eight cases had myelomeningocele and three cases miscellaneous diagnoses. Thirty-four cases had functioning shunts. All patients had been followed from one to 24 months post-operatively. An analysis of the failures was given.

Chemopallidotomy and Chemothalamotomy in Parkinson's Disease

B. BROAGER and T. NORHØLM (Copenhagen) reported on a series of 100 consecutive patients with Parkinsonism treated by chemopallidotomy or thalamotomy. Cooper's technique was followed except that small successive injections were given instead of balloon inflation. All patients were operated on before April, 1960, the follow-up time being one to four years.

The average age was 56 years, 37 being over 60. Sixty-three patients had unilateral and 37 bilateral treatment; several patients had more than two lesions. Five patients died within eight weeks of operation and were considered surgical mortality. Some of these went into coma after pneumography and introduction of the cannula into the medial pallidum. Although no injections were given and the cannula withdrawn the following day, coma lasted until death. Necropsy showed no evidence of haemorrhage but severe diffuse degeneration in the basal ganglia. Thirteen patients died after longer periods of time and four could not be traced. The remaining 78 patients were followed up.

The immediate post-operative effect, lasting more than three months, was very good or good in 85 patients but in 10 the operation had a poor effect or no effect. The effect on rigidity was very good or good in 80 patients (84% of 95 patients who had rigidity). There was little or no effect in 10 patients.

Severe complications included three cases of deep haematoma with lasting hemiplegia (two of these were included in the late deaths). In several patients with bilateral treatment a disturbance of speech was noticed after the second operation, mostly an aphonia.

In the follow-up at one to four years a good or very good effect on tremor was found in 58 (60%), 10 had recurrence of tremor, and 13 had died. A very good or good effect on rigidity was seen in 61 patients (66% of those with rigidity) and in 12 it showed little or no effect.

An estimate had been made of the overall condition of the patients and it was found at follow-up that 45 cases were benefited, 21 were no better than before operation, and 12 were worse. In addition 18 patients had been improved for substantial periods of time but had later deteriorated from progression of disease (13) or had died of the disease (2) or of some other illness (3). In all, 63 (66%) were improved for long periods of time or were still improved at follow-up. Amongst the 32 patients not improved in their overall condition, including the five operative and seven late deaths, 15 were completely or

severely oligokinetic before operation and four others were prematurely aged and partly demented. Such patients would not be operated on at the present time. The best results would be obtained by operating on good-risk patients and on one side only, but in spite of this, several bad-risk patients in the series had had good and lasting results from treatment.

The Use of Subdural Air Injections in the Selection of Patients with Subfrontal Fractures for Operation

ANTONY JEFFERSON and NORMAN LEWTAS (Sheffield) stated that because meningitis resulting from anterior fossa fractures might be fatal in spite of prompt treatment, it was vital to recognize the presence of dural lacerations adjacent to the nasal cavity or to the frontal, ethmoidal, or sphenoidal sinuses.

The surgeon treating anterior fossa fractures might need to operate before rhinorrhoea had been observed or meningitis had occurred. In a series of 13 patients who had required dural grafts in the frontal region, three had never experienced rhinorrhoea, no intracranial air had been observed, and meningitis had not developed. The authors described and illustrated a method by which air, injected subdurally through a frontal drill hole, might be used to demonstrate adhesions between the floor of the skull and the under surface of the frontal lobe. In the presence of subfrontal fractures, such adhesions corresponded to the site of dural defects.

By means of subdural injections the surgeon might sometimes be able to satisfy himself that there was no dural defect, and hence an unnecessary operation could be avoided. Absence of a dural defect might be demonstrated even though, in the initial phases, air had been detected within the skull, or the radiological features of the fracture made an accompanying dural laceration highly probable. Examples of these two situations were illustrated.

It was emphasized that the present contribution represented a preliminary communication.

Lumbar Myelography with Water-soluble Contrast

H. H. JACOBSEN (Copenhagen) reported on the use of Abrodil in lumbar myelography. He said that in cases with cervical or thoracic localization he used gas myelography except in patients who were obese, had pronounced scoliosis, or cardiac disease. In these cases Pantopaque was used.

In using Abrodil for lumber myelography a spinal anaesthetic was necessary and blood pressure must be checked during and after operation. During the period 1959-60, 200 such examinations had been carried out. In 29 cases the examination was reported as normal; in three of these a subsequent operation was performed, and in only one was a disc prolapse found. In 142 cases a disc prolapse was diagnosed and 117 were operated on. A prolapse at the level expected was found in 104 cases and prolapses at two levels which had been predicted in five cases. Protrusions were found in three and only exostoses without prolapse in two. In three cases only arachnoiditis or scar tissue was found. There were no negative explorations. In 18 of the 142 myelographies only a shortening of the root sheath was found without filling defect in the contrast column. Ten of these were operated on and prolapse found at the expected level. In 19 cases a protrusion was diagnosed and of eight patients operated on only three showed a prolapse. In the remaining 10 cases miscellaneous conditions were diagnosed. One had scar tissue and five sacral root cysts. Two had cystic malformations (one verified) and one had a tumour (verified). One had a large terminal sac which made judgment as to disc prolapse impossible and proved to have a prolapse at operation.

Complications occurred in 14 cases (7%) but none were permanent. Three patients had slight headache; 10 had severe pain in the legs or perineal region, and seven of these recovered at once after Pethidine. One patient had an epileptic fit 24 hours after myelography.

Local Cooling as an Adjunct to Cerebral Operations

K. KRISTIANSEN (Oslo) and N. M. DOTT (Edinburgh), in presenting a preliminary report on a case in which local cerebral cooling was employed, referred briefly to the history of hypothermia and its recent use as an adjunct to cerebral surgery. They expressed the view that profound cooling was desirable, and contrasted its achievement in the brain by the method of profound general cooling involving cardiac by-pass with profound local cerebral cooling involving carotid by-pass only. The pioneer work had been done by K. Kristiansen in developing and practising the latter method with excellent results.

The case reported was one of right Sylvian arteriovenous malformation in a youth of 16 years. The fistulous flow was exceptionally large and there were special difficulties of access to the vessels concerned. Dr. Kristiansen had been consulted and he and Professor Semb of Oslo had generously agreed to receive the patient, Professor Dott, and a team of four others, in order that the operation would be carried out in Oslo with the benefits of the local cerebral cooling technique developed there. This was successfully accomplished in December, 1960. A slight residual hemiparesis was believed to be due to arterial spasm and temporary local ischaemia in the field of the middle cerebral basal perforating arteries proximal to the lesion and to the site of temporary occlusion of the middle cerebral artery. The lesion was probably incurred by reason of persistent spasm of these small branches after the cold perfusion had ceased and the brain had been re-warmed. Possible means to overcome this risk by the local application of papaverine to the arterial walls was discussed. It was suggested that this adjunct to cerebral surgery had many advantages and that it could and should be perfected by further laboratory work and by cautious clinical application.

BOOK REVIEWS

Visual Field Defects After Penetrating Missile Wounds of the Brain. By Hans-Lukas Teuber, William S. Battersby, and Morris B. Bender. (Pp. xi + 143; 55 figures. 38*s*.) Cambridge, Massachusetts: Harvard University Press (London: Oxford University Press). 1961.

Missile wounds of the brain in the Russo-Japanese War and the two world wars have provided much information about the visual pathways in the cerebral hemispheres, and it is therefore particularly valuable to have this contribution from these American observers who have studied visual problems in brain-wounded subjects for 15 years or more. They review the literature about the anatomy of the visual radiation and striate cortex but add relatively little that is new to this subject. They discuss the mechanism of macular sparing and put yet another nail in the coffin of the theory of bilateral macular representation in the cortex. They stress that in their experience, though not in that of most others, incongruous field defects are very common in lesions at all levels of the visual pathways, including the striate cortex, and recommend that this point should receive special attention in future studies.

Probably the most important chapter is that which deals with 'functioning' as opposed to plotted fields. Here are assembled the authors' findings on fluctuation, extinction, completion, and the phenomena which occur when vision returns during convalescence to an area which was densely scotomatous in the acute stage. At first an undifferentiated sensation of light is appreciated, then a moving light can be distinguished from a stationary one, although rate and direction of movement are not recognized, and then objects can be orientated in space about the time at which indistinct contours are visible. The authors also describe the role of flicker perimetry and of measurements of dark adaptation in demonstrating minimal losses or minimal remnants of function. They discuss the various types of visual function which may be lost or preserved in an abnormal part of the field. They conclude that there is no good evidence of separate cerebral localization for the various functions, but that there is a hierarchy among them according to which they are lost or regained in a certain order. A section on visual hallucinations in brain-wounded subjects includes a cautionary tale of a patient who unwisely admitted to seeing little horses and who spent the next two years in hospital with the diagnosis of schizophrenia.

Evaluation and Management of the Brain-Damaged Patient. By Jerome S. Tobis and Milton Lowenthal. (Pp. xii + 109; 33 figures. 48*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

The authors of this book are engaged in rehabilitation and in various aspects of physical medicine. A considerable attempt is made to explain the physiological effects of brain damage on muscles and movement, but there are many inaccuracies. Those who attempt to select snippets of physiological knowledge in this complex field encounter many pitfalls.

The Structure and Function of Muscle. Edited by G. H. Bourne. Volume I: *Structure* (Pp. 472; 137 figures, 24 plates, 9 tables. £5 0*s*. 0*d*.; $14.00); Volume II: *Biochemistry and Physiology* (Pp. 593; 73 figures, 1 plate, 29 tables. £5 18*s*. 0*d*.; $16.50); Volume III: *Pharmacology and Disease* (Pp. 489; 46 figures, 20 plates, 4 tables. £5 7*s*. 6*d*.; $15.00). New York and London: Academic Press. 1960.

Volume I is the first of three to be published on muscle considered both structurally and functionally. Dr. G. H. Bourne has been able to obtain the help of a number of distinguished experts in various fields and they have written chapters on the different aspects concerned.

This volume contains some excellent articles on electron microscopy, notably one by Huxley and Hanson on the molecular basis of contraction, who describe the sliding filament hypothesis. Two chapters, one by H. Stanley Bennett on the structure of muscle and the other by Sjöstrand and Anderson-Cedergren, are outstanding. Hanson and Lowy give an exhaustive and critical survey of the contractile apparatus in the muscles of invertebrates. Other intensely interesting chapters are on tissue culture (Murray), the motor end-plates (Couteaux), and the muscle spindles (Cooper), but it is not possible to mention all by name.

The illustrations are very good, particularly the electron microscope ones, but a few do not indicate the magnification and some show artifacts.

This book will have to be read by all interested in muscle and can be recommended.

Volume II provides a detailed and highly specialized account of the functional rather than the structural aspects of muscle. The chapters are therefore mainly devoted to biochemistry, biophysics, and physiology and they are most stimulating. The reviewer especially enjoyed the chapters by Drs. Szent-Györgyi and Needham on biochemistry and Dr. Nachmansohn on the neuromuscular junction.

Volume III deals with aspects of pharmacology and disease and covers a wide field in both animal and human muscle. The clinical pathologist will be helped by a number of these chapters. There is one by Dr. Bosanquet, Professor Daniel, and Dr. Parry on the histological changes in various conditions affecting muscle and this chapter is very well illustrated.

Chapters on ageing changes in muscle by Dr. Rubinstein, on post-mortem changes by Dr. Bendall, which is especially devoted to theories of the rigor process, are also excellent. Drs. Beckett and Bourne have described their findings of various enzyme systems by histochemical studies in some diseases but, as they say, these cannot be regarded as an authoritative collection of facts. Virus and parasitic infections of muscle are dealt with in detail as are the effects of nutritional deficiency in animal muscle. The histological features in muscle regeneration and repair are found in another chapter, but unfortunately they are not illustrated.

The clinical and the genetic aspects of diseases affecting muscle are described in two excellent chapters by Drs. Henson and Walton respectively. There is, however, no reference to levels of serum enzymes nor to the myopathy in which there is a deficiency in phorphorylase (McArdle's disease). Finally Dr. Szent-Györgyi typically comments briefly on muscle and its contractile function.

The three volumes are a fairly exhaustive record of the position concerning the structure and function of muscle as it existed a few years ago, for in the last volume there are few references to papers of the last two to three years. The production is good even though most of the illustrations would have been better if they had been larger and it is unfortunate that in places names are mis-spelt.

Physiological Reviews, Vol. 40, Suppl. No. 4, Pt II: Proceedings of a Symposium on Central Nervous System Control of Circulation. Edited by Ludwig W. Eichna and Lt. Donald G. McQuarrie. (Pp. viii + 311; illustrated. $5.00). Washington, D.C.: The American Physiological Society. 1960.

The symposium of which the proceedings are reported in this issue was intended to provide a common forum for neurophysiologists and for physiologists who work mainly on the cardiovascular system. The result is an authoritative statement of current views on the nervous control of the circulation. It contains contributions on the anatomy of cardiovascular reflexes, and on the physiological part played by the brain-stem, hypothalamus, and cerebral cortex in control of the cardiovascular system. Other sections deal with the reflexes controlling the circulation to the brain, the kidney, and the skin, and the final sections describe conditioned cardiovascular reflexes. It is now clear that the veins are extremely active and not merely passive tubes which return the blood to the heart. Considerable interest is now being taken in the reflexes controlling this activity of the veins, and a valuable section is devoted to studies of these reflexes in isolated venous segments.

Little is said about changes occurring in disease, but it is essential for the clinician to understand normal mechanisms if the circulatory phenomena occurring in, for instance, tabes and polyneuritis, are to be understood.

Nerve Endings in Normal and Pathologic Skin. By R. K. Winkelmann. (Pp. viii + 195; 42 figures. 60*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

This is an excellent monograph on a subject which has recently undergone an upheaval. For most of the present century, a theory of the physiology of cutaneous sensation has been generally accepted, which recognized four primary 'modalities' of sensation, mediated by four distinct types of peripheral nerve ending, each with an independent nervous 'pathway', interrupted, for no known purpose, by a number of 'relay' points. Associated with this theory is the notion that the integument can be divided into a mosaic of sensory 'spots', each of which overlies a specific 'receptor' of one of the four types. This theory has been largely demolished; on the anatomical level, by the demonstration that no correspondence can be found between sensory 'spots' and histologically specific 'receptors'; physiologically, by showing that individual afferent nerve fibres respond to different kinds of 'natural' stimuli; finally, there has been some rough handling of the logical basis of the four 'modalities' and the sensory 'spots'.

The book under review is mainly concerned with the neurohistology of the skin and mucous membranes. The subepithelial plexuses and the forms of nerve terminal are described in detail, with excellent illustrations, mainly photographs of silver impregnations. The author proposes a simple, and very acceptable, classification of cutaneous nerve endings into (1) free ramifications arising from the dermal network, including the more compact terminal arborizations seen in dermal papillae; (2) the basket-like networks around their follicles; (3) mucocutaneous endings, a large variety of compact terminal arborizations, which in the past have given rise to a bewildering array of eponymic terms; (4) Meissner's corpuscles, found characteristically in the papillary ridges of the hand; and (5) the Vater-Pacini corpuscles.

Where the author discusses function, he is less satisfying. It is not his fault that a convincing theory in terms of spatio-temporal patterns of impulses, and central re-coding of these, has not yet been worked out; on the other hand, he appears to accept too readily the classification of sensation into the four traditional 'modalities', and is guilty of verbal confusion when he uses a word such as 'touch' to cover a physical stimulus at the one end, and a sensation at the other. The fact that a Pacinian corpuscle is supplied by a nerve fibre which becomes active when the corpuscle is squeezed does not imply that these organs function as 'pressure-receptors', or that they have any concern in sensation. The alternative view, that they serve to signal local changes in the blood circulation, and form part of an autonomic reflex mechanism, is at least equally plausible. Whatever the facts may be, the author is not helping the cause of psycho-physical correlation when he speaks (on page 80) of these organs as 'perceiving' pressure changes in the tissues.

The chapter on the changes associated with disease is useful in pointing out how little is at present known about this subject. The more fundamental question of the degree to which peripheral nerve endings are labile, and undergo progressive and regressive changes during normal adult life, will probably require to be answered before the problems of peripheral neuropathology can be cleared up.

Structure and Function of the Cerebral Cortex: Proceedings of the Second International Meeting of Neurobiologists, Amsterdam, 1959. Edited by D. B. Tower and

J. P. Schade. (Pp. xi + 448; illustrated. 85*s*.) London: D. Van Nostrand. 1960.

This conference collected together research workers on the anatomy, physiology, and biochemistry of the cerebral cortex, and this report of the proceedings gives much information regarding present knowledge. The physiological mechanisms of the hippocampus and the microchemistry of glia and nerve cells describe many important advances in knowledge.

Anatomie des Menschen. Ein Lehrbuch für Studierende und Arzte. By H. Braus; Foreword by C. Elze. Band III: **Periphere Leitungsbahnen. II. Centrales Nervensystem Sinnesorgane**, 2nd ed. (Pp. viii + 832; 545 figures. D.M. 69.-.) Berlin-Wilmersdorf: Springer-Verlag. 1960.

The first volume of Braus's Anatomy deals with the locomotor system, the second with the viscera. This, the third volume, covers the peripheral nervous and vascular systems (385 pages), the central nervous system (235 pages), and the sense organs, including the skin (189 pages).

The writer of a textbook of anatomy has a difficult problem in deciding how much space should be devoted to the central nervous system. If he is to cover the ground in detail, this section is likely to outweigh the whole of the rest of the work. If he summarizes another kind of disproportion arises, illustrated in this book by the fact that 47 pages, with 25 pictures, are devoted to the nervous and vascular supply of the leg but only two and a half pages, with one picture, to the vessels of the spinal cord and brain-stem.

Another difficulty arises from the peculiar methods used by neuroanatomists and neurophysiologists in their task of tracing the connexions of different parts of the nervous system. On this subject there is a mass of detailed information, some of it well-established, some probable but unconfirmed, some contradictory, and much highly disputable. This textbook seldom indicates the degree of reliability of the information it imparts; and there are no references to the work on which the information is based.

The disparity between the section on the peripheral nervous and vascular systems, which is excellent, and that on the central nervous system, which is unsatisfactory, might have been overcome by leaving aside the subject of neural connexions, and concentrating on the gross topography, with detailed dimensions, fuller descriptions of vascular arrangements, and more reference to the techniques of angiography and pneumoencephalography.

The book is handsomely produced, and beautifully illustrated. From this point of view, it would repay study by the editors of English textbooks of anatomy.

Markhaltige Faserverbindungen am Hirnstamm der Katze. By S. Bürgi and V. M. Bucher. (Pp. iv + 127; 49 figures. D.M. 39.60.) Berlin-Wilmersdorf: Springer-Verlag. 1960.

The book represents a systematic neuroanatomical record of the behavioural experiments by W. R. Hess on the brain-stem of cats followed by subsequent lesions in the structures stimulated. As the stimulation experiments have been recorded on films which, together with the brain sections, are available for study at the Hirnbiologische Sammlung at Zurich, this publication of Marchi-stained series is of considerable value in relating brain function and structure. The results have been discussed in a detailed way with the experimental studies of other authors, and for this reason an up-to-date account of the relevant literature is given. The senior author (a clinical neurologist) has integrated experimental results with clinical observations, thus adding to the neurological interest and scope of this book. Both authors are to be congratulated on their painstaking, extremely well-documented work, providing a great source of information on brain-stem structure and function available to the English-speaking neurologist, as each chapter has an extensive English summary.

Handbuch der Neurochirurgie, Vol. 4, Pt 1. Edited by H. Olivecrona and W. Tönnis. (Pp. xvi + 782; 271 figures. D.M. 386.-.) Berlin-Göttingen-Heidelberg: Springer-Verlag. 1960.

The fifth section of this imposing work has now appeared. The formidable book under review forms the first part of the fourth volume, which deals with the symptoms and treatment of space-occupying intracranial lesions. This part is concerned with general surgical technique, deformities of the skull and brain, lesions neoplastic and inflammatory of the skull bones, infestations and infections by metazoan parasites and fungi, and the problem of hydrocephalus. Space-occupying lesions of the brain itself, neoplasms of its coverings, abscess, and haematoma are clearly to be dealt with in the other two parts yet to appear.

The survey of general neurosurgical procedures by F. J. Irsigler is informative and one must compliment the author on a more than adequate performance of a task that is peculiarly difficult of execution in any book that aims at being comprehensive. Selection of material must indeed be a problem here. The approach naturally results in a tendency to list too much for fear of omitting something of importance. However, the author has succeeded in giving a most readable account of the basic techniques, with interesting sections on pre- and post-operative care and complications, and even one on dealing with the relatives.

Professor Gerlach deals exhaustively with congenital malformations of the skull and brain, and with G. Simon covers that most complicated and controversial subject, the recognition, diagnosis, and treatment of tumours and inflammations of the skull bones. Then Dr. Kleinsasser describes the tumour pathology of the skull and orbit in a magnificent monograph of 170 pages of which not less than 44 are devoted to a truly monumental bibliography. Not content with this effort, with another coadjutor Dr. Kleinsasser contributes another article on other skull diseases of surgical importance.

One of the most interesting articles in this volume is the monograph on the operative treatment of hydrocephalus by Professor T. Riechert and W. Umbach which brings together an enormous amount of information. Here we find a note on every method of treatment of hydrocephalus that has ever been suggested. A common

difficulty in treatises of this kind is that though one is referred to a multitude of surgical procedures, it seems that there is a reluctance to advocate any definite measure and, therefore, relatively little attempt is made to evaluate the methods described or to suggest reasons to support one in preference to another. Those interested in the treatment of hydrocephalus will, however, find here an invaluable historical survey in which it is not difficult to separate the useful contributions to surgery from the many brilliant suggestions which have proved less brilliant in practice. It is a little surprising to find no reference to ventriculoatriostomy by the Spitz-Holter valve, which has certainly become the method of choice in this country for most communicating cases.

A short but very interesting summary of anaesthesia in neurological surgery comes from the hand of Dr. Torsten Gordh.

The production, printing, and illustrations are of the high standard we expect from a handbook emanating from such publishers. The references to the literature are throughout copious, widely selected, and admirably set out, and the indexes are entirely adequate. Certainly we will look forward to each new volume as it appears.

Principles of General Neurophysiology Relating to Anaesthesia and Surgery. By Barry D. Wyke. (Pp. ix + 136; 26 figures. 21*s*.) London: Butterworth. 1960.

It is obvious that the intelligent use of drugs such as anaesthetics requires some knowledge of what is known regarding the anatomy, physiology, and pharmacology of nerve cells. This little book provides this information in a way that will be appreciated, especially by post-graduate students concerned with anaesthesia.

Le Foie Alcoolique de L'Hépatite a la Cirrhose Alcoolique. By P. Etienne-Martin and Cl. Klepping. (Pp. 162; 7 figures and 10 tables. N.F. 20.-.) Paris: Masson & Cie. 1960.

Alcoholism in France is a serious problem, for in 1956 deaths from cirrhosis of the liver were more than 14,000, and from acute alcoholism more than 6,000. Drs. Etienne-Martin and Klepping, both of Dijon University and Hospital, have written an extremely able monograph on the liver in alcoholism. In the main they deal with cirrhosis but also to some extent with the earlier changes to be found in the liver, from aetiological, pathological, clinical, and therapeutic aspects.

Hepatic coma, the peripheral neuropathies, and the psychological aspects are included in the discussion.

The field covered is very wide and the two authors have drawn extensively upon their experience as well as upon the writings of all the well-known authorities. This volume must be read by all interested in liver disease as well as those concerned with the psychological aspects of intemperance and it can be thoroughly recommended.

The volume possesses some defects which are not uncommon in some French monographs; there are no references, there is no index, and there is a certain lack of a critical attitude to other writers on this topic.

The Unconscious before Freud. By Lancelot Law Whyte. (Pp. xiii + 219. $4.50.) New York: Basic Books. 1960.

That the mind can function independently of conscious volition or control has been realized ever since man became aware of his dreams, and that mental activity beyond consciousness continues in the waking state has been appreciated ever since introspection, analysis, and the association of ideas became the methods of metaphysicians and philosophers in the seventeenth century. From an entirely different field, study of autonomic and reflex nervous action in the eighteenth and nineteenth centuries provided a neurological analogy if not basis for the concept and led to the dispute whether it should be regarded as unconscious mentation or cerebration. In the twentieth century Freud discovered the mechanisms of the unconscious and its links with conscious mind and laid the groundwork of its application to the understanding of normal mental development and mental illness. The concept of an unconscious therefore has very ancient roots, and its history may be traced in the writings of philosophers, physiologists, physicians, and poets, in fact in all who have ever concerned themselves with the study of mankind. The author of this book (described as 'the eminent thinker' on the dust jacket) has gathered scattered allusions to the subject from European writings after 1600. Unfortunately he lacks the specialist vantage point (or bias) and in consequence is handicapped in distinguishing the important from the unimportant, the incidental from the vital. His thesis 'that Freudianism as we know it it is but one crucial step in the development of man's knowledge of himself' is of course a truism, and this attempt to show that Freud's 'originality was in some respects less than he and others have imagined' will not detract from it. The book leaves the feeling of an urgent need for an authoritative exposition of psychological and psychiatric sources.

Psychophysiologic Approach in Medical Practice. By William W. Schottstaedt. (Pp. 352. 60*s*.; $8.00.) Chicago: The Year Book Publishers. 1960.

It is unfortunate that this excellent though elementary book has such a forbidding title which may cause it not to reach the wide audience it deserves. It has been written primarily for medical students and practitioners who are not specialists in psychiatry. It aims to provide a framework of concepts concerning physiological and mental mechanisms and emotional, social, and cultural forces. On the basis of these concepts the author describes the ways in which emotional disturbances arise and seeks to develop a basis for treating patients with ailments associated with emotional disturbances.

The author does this and more. He describes clearly how the emotional disturbances of many patients can be handled by the general practitioner or the general physician without recourse to the specialist psychiatrist, dealing with patients' problems along commonsense lines and acting not only as technician but also as counsellor. The author's wide experience and humanity pervade the book, and chapters which can be especially recommended are those on 'Interviewing' and the 'Doctor-patient Relationship'. The author indicates when patients with emotional disturbances should be referred to a psychiatrist, but if this book attains the wide popularity it deserves and its approach to patients is accepted, it should reduce the number of patients so referred.

Psychiatrists are often shocked by the way their non-psychiatric colleagues handle their patients, not as a person but as a deranged organ or system and indeed they often have to repair the consequences of such mismanagement. Many non-psychiatrists would benefit from reading this book, and it can be especially recommended to medical students who are still malleable.

The Central Nervous System and Behavior. Transactions of the Third Conference. Edited by Mary A. B. Brazier; sponsored by the Josiah Macy, Jr. Foundation, New York, with the co-operation of the National Science Foundation, Washington. (Pp. 475; 201 figures. $7.50.) 1960.

This conference met at Princeton in February, 1960, under the Chairmanship of Dr. H. W. Magoun. As with its predecessors, the aim appears to have been to bring together men working in a variety of disciplines converging on neurophysiology rather than to hold a genuine symposium built round a particular topic. Indeed, choice of topics appears to have been governed almost wholly by the special interests of the participants, which range from the brain of Neanderthal man to the response of the infant monkey to a surrogate mother. Although it is hard to see much relation between the different themes, the frequency with which leading speakers were interrupted at least suggests that much interest was aroused, and one may hope, some mutual understanding created. It is pleasant to note that two distinguished Russians took part.

Mental Retardation in Infants and Children. By Abraham Levinson (deceased) and John A. Bigler. (Pp. 308; 53 figures. 60*s*.; $8.) Chicago: The Year Book Publishers. 1960.

There is a need for more and better textbooks on mental deficiency, all the greater for the advances which have been made in recent years on a broad front. These have been marked by major improvements in biochemical and cytological techniques, a more biological approach to the problems of deficiency, greater understanding of aetiology, and a revolution in methods of training and rehabilitation of patients. One might have expected that all these would have provided rich material for the writing of a new textbook to show new trends and extensions in the field.

The book under review falls somewhat short of such an expectation. The authors set out to cover their subject comprehensively, and their book contains much useful information. Nevertheless this is often very sketchy, as in the chapter on abnormal protein metabolism which, as it stands, would have been better omitted. Important work carried out elsewhere than in the United States, such as that of O'Connor and Tizard on the training of the mentally subnormal, is passed over. The bibliographies at the end of chapters are short, but mention too many minor papers while omitting classical key references. References in the text are not always included in the chapter bibliography. There is no author index.

The material could have been better arranged. The chapter on 'Research' is largely redundant, overlapping with the chapter on 'Etiology and Classification'. No mention is made in the paragraph on the aetiology of mongolism of a chromosomal anomaly, reference to this being confined to six lines at the end of the chapter. Valuable space is taken up with case histories, and with histograms of which the meaning could have been better expressed in a few sentences, while important facts of general interest are omitted. The sections on prophylaxis and medical treatment, in which helpful hints are handed out to the obstetrician and physician, could have been drastically pruned.

Despite faults which deprive it of value for the specialist, the book is both readable and well illustrated, and will be appreciated by those who come new to this field of work. The sections on case taking and physical examination will be a useful guide to those embarking on clinical work with defectives; and the forthright approach to practical problems make it suitable selected reading for nurses and social workers.

The Role of Speech in the Regulation of Normal and Abnormal Behaviour. By A. R. Luria. (Pp. 110; illustrated. 50*s*.) London, Oxford, New York, Paris: Pergamon Press. 1961.

The study of behavioural responses in children provides an enormous amount of information regarding brain mechanisms, and Russian experimental psychologists have studied this subject by observing the young child's reaction to simple experimental situations. Professor Luria reported some of these studies in lectures he gave in London in 1958, and this expensive little book consists of a translation of these lectures. Of special interest is the demonstration that speech from the observer, or by the child himself, has a tremendous influence on the accuracy of a simple motor response. The power of speech is certainly overwhelming as regards the development of behavioural patterns.

The Kybernetics of Natural Systems: A Study in Patterns of Control. By D. and K. Stanley-Jones. (Pp. xii + 145. 42*s*.) London, Oxford, New York, Paris: Pergamon Press. 1960.

This small and, for its length, extremely expensive, book is highly recommended in a preface by Dr. Norbert Wiener, who may perhaps be regarded as the father of cybernetics. Its aim is to illustrate the application, in a non-quantitative way, of some of the principles of control engineering to neurophysiology and psychology. It may be said at once that the authors, except in a last chapter on human society, stick to this task more consistently and in more concrete terms than is common in many popular and semipopular works in this field. They discuss with some considerable show of detail a vast number of physiological and other biological mechanisms in cybernetic terms, and perusal of the book may well encourage many readers to assimilate these concepts into their own thinking. It is a pity, therefore, that only a selection from the cybernetic repertoire of basic ideas is used. Questions of the nature and the role of communication in the nervous system are deliberately avoided, and while the notion of 'information' is not introduced, the disturbing expression 'neural dynamic' is coined, hardly defined, and widely employed. The cybernetic principles with which

the book deals are largely confined to those of negative and positive feedback (the latter word here—rather gratuitously as it seems—replaced by 'refection') and the operation of these to produce, on occasion, 'runaway to zero' and 'runaway to maximum'. These ideas hardly provide sufficient equipment for the informed interpretation of any physiological or psychological function. While often superficially enlightening, there is some danger of their being ultimately confusing. The physiological detail, too, is often too sketchily presented to enable the worth of the argument to be judged.

It must be emphasized, however, that in the course of these not always satisfying discussions a number of interesting and thoughtful ideas are thrown up. It is for these, rather than as an authoritative exposition, that the book ought to be read.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Hypothermia for the Neurosurgical Patient. By Antonio Boba. (Pp. vii + 124; 49 figures. 48*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

Cerebrospinal Fluid Dynamics in Health and Disease. By David Bowsher; Foreword by I. Newton Kugelmass. (Pp. xi + 80; 22 figures. 38*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

Lehrbuch der Psychiatrie, 10th ed. By Eugen Bleuler; Foreword by Manfred Bleuler. (Pp. xvi + 629; 121 figures. DM 56.-.) Berlin-Göttingen-Heidelberg: Springer-Verlag. 1960.

A Ciba Foundation Symposium on **Adrenergic Mechanisms.** Editor for the British Pharmacological Society: J. R. Vane; Editors for the Ciba Foundation: G. E. W. Wolstenholme and Maeve O'Connor. (Pp. xx + 632; 163 figures. 70*s*.) London: J. & A. Churchill. 1960.

The Pathology of Cerebral Palsy: The Causes and Underlying Nature of the Disorder. By Abraham Towbin. (Pp. xi + 206; 70 figures. 64*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

Parkinsonism: Its Medical and Surgical Therapy. By Irving S. Cooper. (Pp. xii + 239; 111 figures. £6 12*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1961.

Speech Therapy in Cerebral Palsy. By Merlin J. Mecham, Martin J. Berko, and Frances Giden Berko. (Pp. xi + 307; 71 line drawings. 80*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

The Tutoring of Brain-Injured Mentally Retarded Children. By James J. Gallagher; Foreword by Samuel A. Kirk. (Pp. xv + 194; 18 figures. 54*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

Evaluation of Drug Therapy. Edited by Francis M. Forster. (Pp. xxiv + 167. $4.00.) Madison: The University of Wisconsin Press. 1961.

Learning Theory and the Symbolic Processes. By O. Hobart Mowrer. (Pp. xiii + 473; illustrated. 68*s*. ($8.60).) London and New York: John Wiley. 1960.

M.R.C. Special Report Series No. 299: **Cysticercosis: An Analysis and Follow-up of 450 Cases.** By H. B. F. Dixon and F. M. Lipscomb. (Pp. vi + 58; 4 figures. 6*s*. 6*d*.) London: H.M.S.O. 1961.

Nerves, Brain and Man. By John Grayson. (Pp. x + 243; 20 figures. 25*s*.) London: Phoenix House Ltd. 1961.

Pain. By F. J. J. Buytendijk. (Pp. 190. 25*s*.) London: Hutchinson. 1961.

Psychiatrie: Ein Lehrbuch fur Studierende und Ärzte, 5th ed. By Kurt Kolle. (Pp. xii + 418; 36 figures. DM 29.80.) Stuttgart: Georg Thieme. 1961.

The Neural Basis of Human Behavior. By Harold Saxton Burr. (Pp. ix + 260; 8 figures. 60*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Thomas. 1960.

Medical Staffing Structure in the Hospital Service. Ministry of Health, Department of Health for Scotland: Report of the Joint Working Party. (Pp. v + 89; 5 figures. Price not stated.) London: H.M.S.O. 1961.

Special Hospitals. Ministry of Health: Report of Working Party. (Pp. 23. 1*s*. 6*d*.) London: H.M.S.O. 1961.

Essentials of Neurology. By John N. Walton. (Pp. xvii + 422. 30*s*.) London: Pitman Medical Publications. 1961.

Scientific Aspects of Neurology: Leeds Neurological Sciences Colloquium 1959-60. Edited by Hugh Garland. (Pp. xi + 264; 86 figures, including 15 colour plates. 50*s*.) Edinburgh and London: E. & S. Livingstone. 1961.

Thinking and Psychotherapy: An Inquiry into the Process of Communication. By Harley C. Shands. (Pp. xvi + 319. 46*s*.) Harvard University Press (London: Oxford University Press). 1961.

Memory, Learning and Language [University of Saskatchewan Jubilee Symposium]. Edited by William Feindel. (Pp. x + 69; 25 figures. 16*s*.) Toronto University Press (London: Oxford University Press). 1961.

Anorexia Nervosa: Its History, Psychology, and Biology. Edited by Eugene L. Bliss and C. H. Hardin Branch. (Pp. vii + 210. Price not stated.) New York: Paul B. Hoeber. 1960.

The Role of Speech in the Regulation of Normal and Abnormal Behavior. By A. R. Luria. (Pp. 110; illustrated. 50*s*.) Oxford: Pergamon Press. 1961.

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THE RECORDING OF LATERAL POPLITEAL NERVE ACTION POTENTIALS IN MAN

BY

R. W. GILLIATT, H. V. GOODMAN, and R. G. WILLISON*

From the Institute of Clinical Research, the Middlesex Hospital Medical School, and the Department of Applied Electrophysiology, the National Hospital, Queen Square, London

It has been shown by Dawson and Scott (1949) that when the median or ulnar nerve is stimulated with a brief shock at the wrist an action potential can be recorded from the nerve at a higher level in the arm through electrodes placed on the skin over the course of the nerve. This technique has proved to be of considerable practical value in the assessment of patients with ulnar nerve lesions at the elbow (Gilliatt and Thomas, 1960).

The advantages of recording the nerve action potential are twofold. In the first place, the potential depends upon the passage of a synchronous volley of impulses under the recording electrodes, and it is thus highly sensitive to dispersion of impulses in different fibres of the nerve. In this way abnormalities of the nerve action potential may be detected when the degree of nerve damage is insufficient to affect conduction velocity in all the constituent fibres. The technique is thus more sensitive than conventional estimation of motor conduction velocity in which measurements of latency are made for the fastest surviving fibre. The second advantage of recording from the nerve itself is that impulses in sensory fibres make a substantial contribution to the action potential. The relative contributions of motor and sensory fibres vary in different nerves, but for the median and ulnar nerves it has been shown by Dawson (1956) that a substantial afferent volley in sensory fibres can be obtained by stimulation below or close to the motor threshold. Recording the nerve action potential may thus be expected to provide information about the behaviour of both motor and sensory fibres in a mixed nerve.

The work to be described in the present paper has been concerned with the recording of nerve action potentials from the lateral popliteal (peroneal) nerve. In general we found lateral popliteal nerve action potentials to be smaller than those seen in the upper limb but, once initial technical difficulties had been overcome, the method proved to be of considerable practical value in the assessment of patients with neurological disorders affecting the lower limbs.

Material and Methods

Observations were made on 39 control subjects. Thirty-five patients with spinal cord or peripheral nerve lesions affecting the legs were also studied.

Subjects were examined lying supine on a couch in a warm room; to minimize cooling they were covered with blankets except for the leg and foot under examination which were loosely wrapped in cotton wool. Complete muscular relaxation of the leg during the recording was best obtained by placing a small pillow or rolled blanket under the thigh so that the knee was slightly flexed; in some cases a slight degree of external rotation at the hip was also helpful. A stimulating cathode was placed over the anterior tibial nerve on the dorsum of the ankle, its position being such that stimulation produced brisk contractions of the extensor digitorum brevis and paraesthesiae radiating into the first interdigital cleft. In some patients with peripheral nerve lesions the normal motor and sensory response to nerve stimulation could not be obtained, and the stimulating cathode was then placed over the expected course of the nerve at the junction of the outer and middle thirds of a line joining the medial and lateral malleoli. A circular pad electrode with a diameter of 1·5 cm. was used as the stimulating cathode. In most experiments the anode was a metal plate 3·5 cm. × 6 cm. strapped to the outer border of the sole, but when simultaneous recording from the extensor digitorum brevis was necessary, the anode was placed behind the lateral malleolus in order to reduce stimulus artefact. These anode positions were chosen for convenience and did not affect nerve conduction times. In each case the stimulus was a condenser discharge with a time constant of 150 μsec. delivered through an isolating transformer (ratio 1 : 1), the peak voltage being continuously variable up to 300 v. In a few experiments, to be described in detail in a later section, two stimuli of independently variable intensity and delay were used.

For recording from the lateral popliteal nerve at the neck of the fibula, both surface and needle electrodes were tried; their relative advantages will be described in

*Clinical research fellow, M.R.C.

a later section. The action potential of the afferent volley was amplified and displayed on one beam of a double-beam oscilloscope. The second beam usually displayed a time-scale, but on a few occasions it was used for a simultaneous display of muscle action potentials from the extensor digitorum brevis. A differential amplifier was used with a time constant of approximately 50 msec. and a high frequency response which was not reduced by more than 3db at 5 kc/s. In a few experiments of the type illustrated in Fig. 5 the time constant was reduced to 15 msec. and the h.f. response heavily cut above 1 kc/s. The effect of these changes on a rectangular pulse is shown in Fig. 5f.

A stimulus repetition rate of 1/sec. was found to be convenient and for photographic recording of the nerve action potential 100 successive sweeps at low brilliance were superimposed. In some experiments a single trigger pulse was used to initiate the sweep, the stimulus, and a millisecond time scale. With this arrangement the onset of the stimulus artefact was not recorded, but latency could be measured directly from the beginning of the time scale which was always visible however large the stimulus artefact. In other experiments a delay circuit made it possible to display the whole stimulus artefact, and in such cases latency was measured from the beginning of the artefact.

Results

Choice of Recording Electrodes.—With a stimulating cathode over the anterior tibial nerve on the dorsum of the ankle, we first attempted to record the action potential of the afferent volley from the lateral popliteal nerve at the neck of the fibula (Fig. 1) using the surface recording electrodes originally described by Dawson and Scott (1949). These electrodes had proved satisfactory in the upper limb but it soon became clear that they were unlikely to be adequate for our purpose; lateral popliteal nerve action potentials were found to be very much smaller than those recorded previously in the arm, and in some normal subjects their amplitude was close to the noise level of the amplifier. Particular difficulty was experienced in patients with obese or oedematous legs, and in order to decrease the distance between the recording electrodes and the nerve trunk, surface electrodes were replaced by two small stainless steel needles (No. 18, hypodermic) placed at right angles to the course of the nerve and inserted to a depth of 1·5 cm. No attempt was made to pierce the nerve sheath, the lower needle being immediately behind the neck of the fibula and the upper needle behind the tendon of the biceps femoris at its insertion. With this arrangement each electrode lay just behind the nerve trunk, the inter-electrode distance varying between 3 and 4 cm. in different experiments.

Direct comparison between surface and needle recording was made in eight control subjects, the inter-electrode distance being similar for the two types of electrode. With buried needles the amplitude of the recorded potential was always greater than that obtained with surface electrodes; the increase in amplitude in different subjects ranged from 11% to 93%, the mean increase for the eight subjects being 42%. A typical result is shown in Fig. 2, trace a (needles) and trace b (surface electrodes) having been made successively without any change in the stimulus applied to the anterior tibial nerve at the ankle. It can be seen that in each case a triphasic action potential was recorded, the main upward deflection of the trace indicating negativity of the lower electrode with respect to the upper one. For the initial upward deflection the amplitude with needle recording (a) was 7·6 μv as compared with 5·4 μv for the surface recording (b). However, when peak-to-peak amplitude was measured in order to

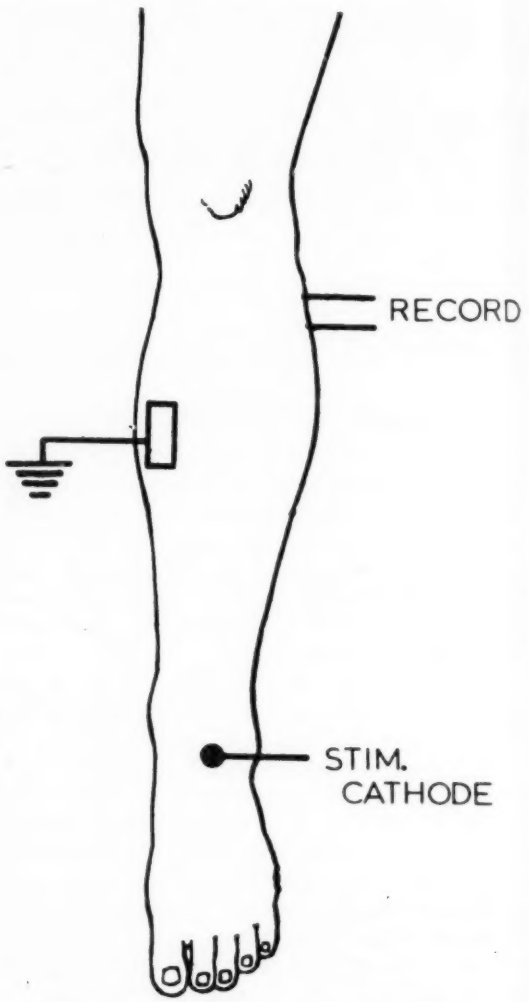

FIG. 1.—Position of stimulating and recording electrodes.

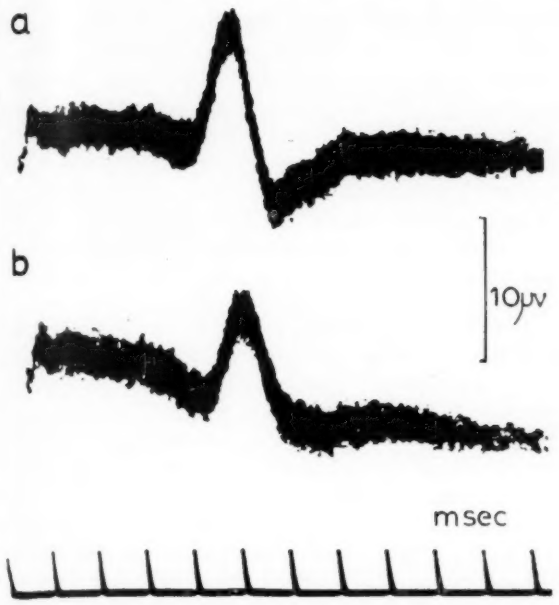

FIG. 2.—Control subject (M.A.). Action potentials recorded from the lateral popliteal nerve using (a) needle and (b) surface electrodes. Stimulus to anterior tibial nerve at the ankle unchanged throughout. One hundred faint traces superimposed.

include the prominent late deflection in the needle record the difference in amplitude was much greater (11·5 μv compared with 6·7 μv). From this and similar experiments it was clear that a substantial increase in the amplitude of the recorded potential could be obtained by the insertion of needle electrodes. For this reason the use of surface electrodes was abandoned and further attention concentrated on the use of implanted needles.

Experiments were then carried out on eight subjects to determine the contribution of each electrode to the recorded potential. For this purpose recordings were first made through a pair of needles at the head of the fibula, after which further recordings were made between each needle of the pair and an indifferent electrode 20 cm. higher on the lateral aspect of the thigh; the stimulus to the anterior tibial nerve on the dorsum of the ankle remained unchanged throughout. Fig. 3a shows the typical triphasic action potential recorded from a pair of fibular needles, the tip of the lower needle being behind the neck of the fibula and the upper needle tip behind the tendon of the biceps femoris at its insertion. As before, an upward deflection of the trace indicates negativity of the lower electrode with respect to the upper one. In Fig. 3b is shown the action potential recorded between the lower needle of the pair and the indifferent electrode, and in Fig. 3c the action potential recorded between the upper of the pair and the indifferent electrode; in both cases the polarity was such that an upward deflection of the trace indicates negativity of the fibular electrode with respect to the indifferent one. From Fig. 3 it is clear that each fibular electrode became active in turn, the time for propagation of the action potential over the 3·0 cm. of nerve between the two electrodes being sufficient to allow

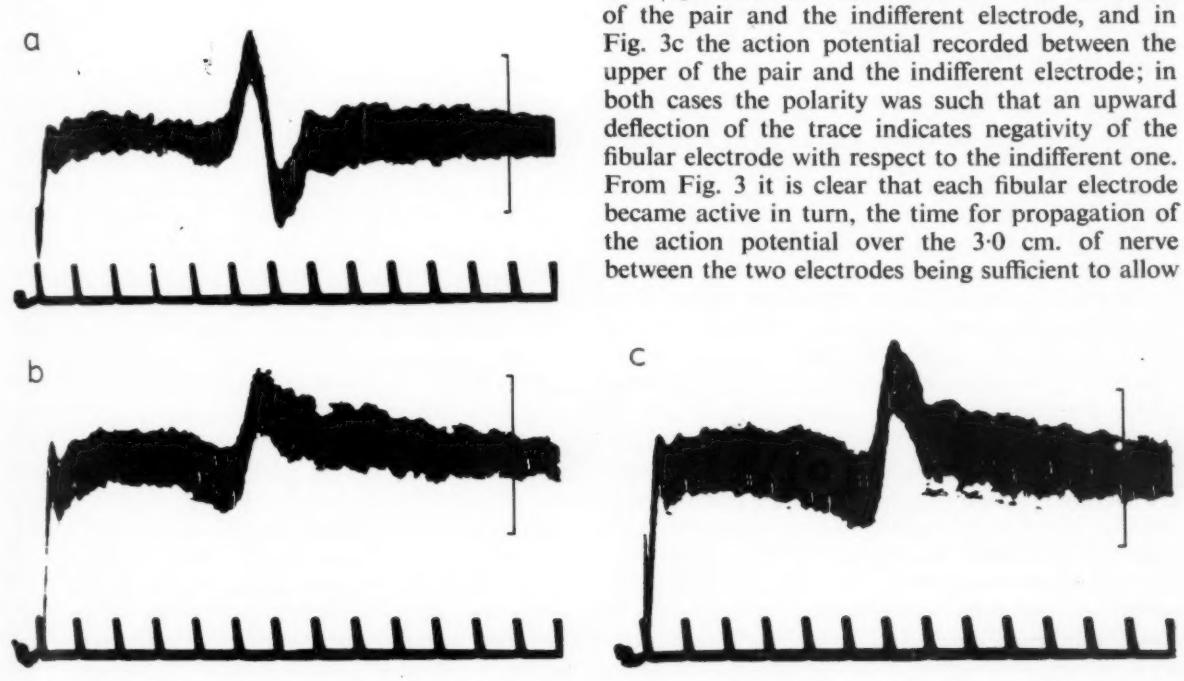

FIG. 3.—Control subject (M.D.). Action potentials from the lateral popliteal nerve; stimulus to anterior tibial nerve at the ankle unchanged throughout.

a. Bipolar recording from two needles 3 cm. apart along the course of the nerve at the head of the fibula.
b. Monopolar recording from lower fibular electrode and distant reference electrode.
c. Monopolar recording from upper fibular electrode and distant reference electrode.

Calibration 10 μv; time scale in msec.; 100 faint traces superimposed.

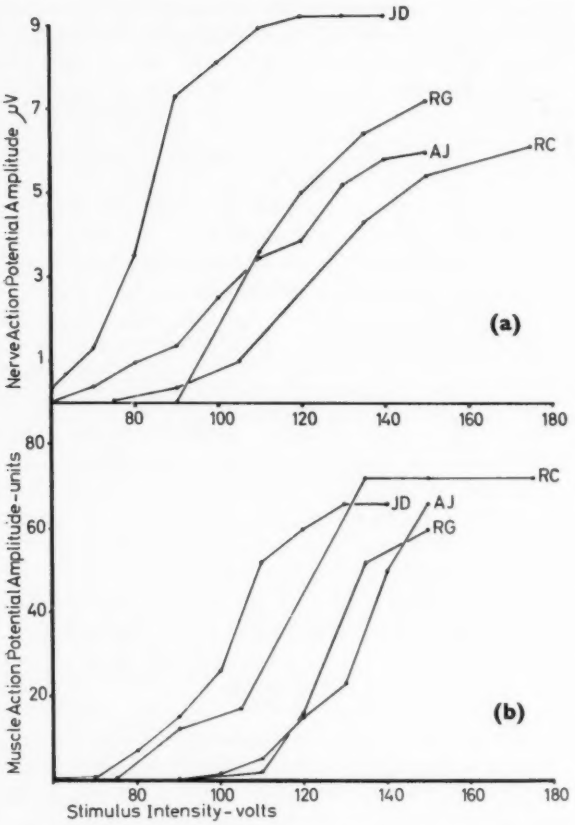

FIG. 4.—Growth of nerve action potentials from lateral popliteal nerve (a) and of muscle action potentials from the extensor digitorum brevis, (b) with increasing intensity of stimulus to anterior tibial nerve at ankle, to show relative excitability of motor and sensory fibres. Curves identified by initials of subjects.

both phases to appear in the bipolar record (Fig. 3a) without significant attenuation.

In the light of this information one can interpret the difference between the surface and needle records shown previously in Fig. 2. The absence of a large third (downward) deflection in the surface record (Fig. 2b) suggests that the upper electrode of the pair was too far from the nerve trunk to make a substantial contribution to the recorded action potential. The needle record (Fig. 2a), on the other hand, shows a prominent third (downward) deflection suggesting that the tip of the upper needle was relatively close to the lateral popliteal nerve as it passed upwards through the lateral part of the popliteal fossa.

From the experiments described above it was concluded that paired needles were probably the most satisfactory electrodes for routine recording. It might be argued that the use of a single exploring electrode at the neck of the fibula with an indifferent electrode on the thigh should be prefered to bipolar recording owing to the simplicity of the recorded waveform in the former case. However, with a single active electrode and an indifferent electrode, much more random muscle activity was recorded than with paired fibular electrodes placed symmetrically and relatively close together. For this reason monopolar records were often spoilt by muscle activity whereas a stable baseline could still be obtained by using paired fibular electrodes in the same patient.

Relative Excitability of Motor and Sensory Fibres.—The effect of varying stimulus intensity was studied in four control subjects. The stimulus was applied to the anterior tibial nerve on the dorsum of the ankle, and the nerve action potential recorded through paired electrodes at the head of the fibula. In each case the muscle action potential was recorded simultaneously from the extensor digitorum brevis through surface electrodes, and displayed on the second beam of the oscilloscope. Results from the four subjects are shown in Fig. 4. Nerve action potential amplitude is shown in Fig. 4a and muscle action potential amplitude in 4b; both are plotted against the stimulus intensity in volts. Individual curves are identified by the initials of the subjects. It will be seen that in subjects J.D., R.G., and A.J. nerve action potentials were present at a stimulus intensity insufficient to excite motor fibres, whereas in subject R.C. the nerve and muscle action potentials appeared together. With increasing stimulus strength a point was reached in subject J.D. beyond which the amplitude of the nerve action potential remained constant. In R.C., R.G., and A.J. nerve action potential amplitude continued to grow throughout the range of stimulus intensity tolerated by the subject, although the increase in size was relatively small at the upper end of the range.

It may be noted that in these experiments three of the four subjects were unable to tolerate maximal stimuli. This was probably due to the fact that each recording involved the superimposition of 100 faint traces so that a full stimulus-response curve was derived from 1,000 or more stimuli. In these circumstances, the repeated use of a stimulus which was even mildly painful was sufficient to prevent the complete muscular relaxation necessary for recording nerve action potentials of small amplitude. However, it is clear from these experiments that in normal subjects the intensity of a stimulus to the anterior tibial nerve can be such that it will excite most of the large fibres in the nerve.

It was mentioned above that in three of the four subjects a nerve action potential could be recorded with a stimulus at the ankle too weak to excite motor fibres in the same nerve trunk, and from

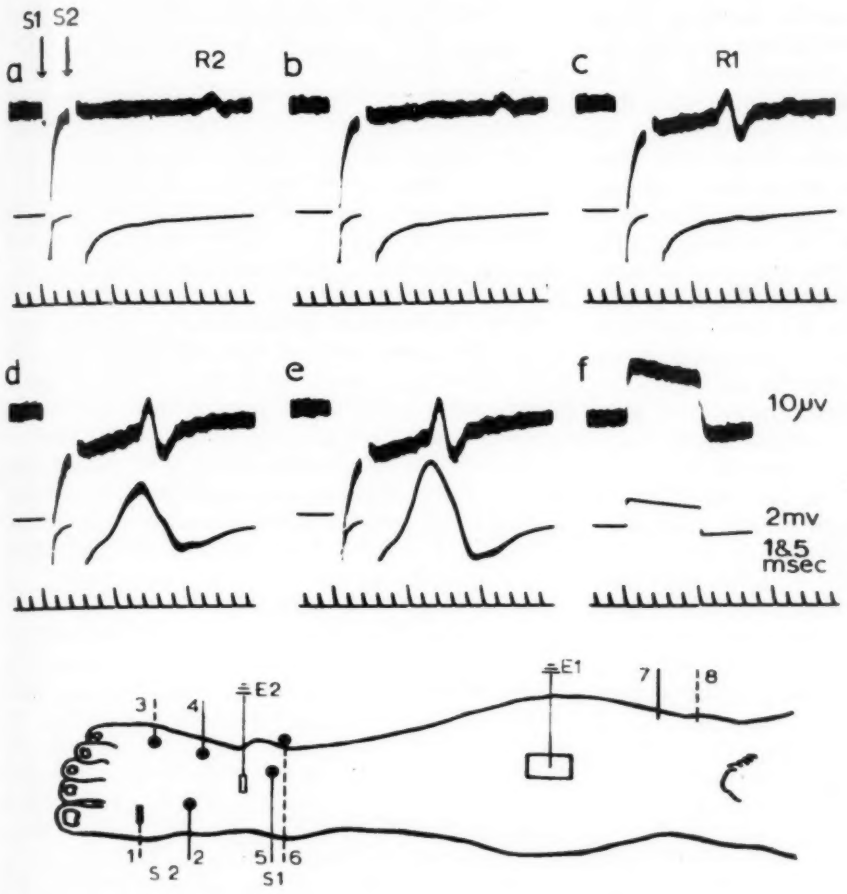

FIG. 5.—Subject R.G. Upper trace shows nerve action potentials recorded through electrodes 7 and 8. Lower trace shows muscle potentials from the extensor digitorum brevis recorded through electrodes 3 and 4. Stimulus S2, producing small potential R2 in upper trace, was unchanged throughout experiment. Stimulus S1, preceding S2 by 2 msec., was gradually increased from subthreshold in a to maximal in e. Nerve action potential R1 appears in c, with diminution of R2, at a time when stimulus S1 at threshold for motor fibres.

Fig. 4 it can be seen that for subjects J.D., A.J., and R.G. the nerve action potential had already reached 11%, 38%, and 50% of maximum amplitude by the time the first motor response was seen. A similar difference in the thresholds of motor and sensory fibres was described by Dawson (1956) in the median and ulnar nerves at the wrist; it was suggested by Dawson that some at least of these low-threshold afferent fibres came not from the muscles but from the fingers. In order to investigate the origin of low-threshold afferent fibres in the anterior tibial nerve, an experiment originally devised by Dawson was adapted for use in the foot. The experimental arrangement is shown under Fig. 5. The anterior tibial nerve was stimulated at the ankle through electrodes 5 and 6, the lateral popliteal nerve action potential and the muscle action potential from the extensor digitorum brevis being recorded simultaneously through electrodes 7 and 8 and 3 and 4 respectively. A further pair of stimulating electrodes 1 and 2 was placed over the cutaneous branch of the anterior tibial nerve on the dorsum of the foot, the distance between the two stimulating cathodes (electrodes 2 and 5) being 10·5 cm. The stimulus S2 was set to follow S1 by an interval of 2 msec., the two stimuli being of identical waveform and duration but of independently variable intensity. The strength of S2 was sufficient to excite the sensory fibres of the anterior tibial nerve and it gave rise to a small action potential R2 recorded through electrodes 7 and 8. This stimulus was kept constant throughout the experiment. The stimulus S1, preceding S2 by 2 msec., was initially too weak to excite either motor or sensory fibres at the ankle but was gradually increased to near maximal during the experiment. The results of one such experiment are shown in Fig. 5a to e, the nerve action potentials being displayed on the upper trace and the muscle action potentials below. In Fig. 5a, S1 was subthreshold and the small nerve action potential (R2) due to S2 is seen with a latency of 9·8 msec. to peak. In Fig. 5b, S1 was sufficient to cause slight irregularity of the upper trace which may be presumed to represent the beginning of a nerve action potential from S1. With a further increase in the strength of S1 this action potential (R1) is clearly seen in c; this record also

shows the first trace of a muscle response. The strength of S1 was further increased in d and again in e. No further change in either nerve or muscle action potential amplitude resulted from increasing S1 beyond this intensity. It will be seen that in c the S1 shock was close to motor threshold so that the nerve action potential R1, whose amplitude was already 50% of maximum, may be assumed to be derived almost entirely from sensory fibres. The question as to whether these fibres are muscle or cutaneous afferents is answered by the effect of S1 on the S2 volley from the dorsum of the foot. The small action potential R2 produced by this volley is clearly seen in Fig. 5a and b, but is largely abolished by S1 in c, indicating that the same fibres were being stimulated at a higher level. Complete blocking of the S2 volley due to a further increase in S1 intensity can be seen in d and e. From this experiment it appears that the cutaneous branch of the anterior tibial nerve can be excited by a stimulus insufficient to excite motor fibres. This does not imply that there is necessarily a true difference in the electrical threshold of the two sets of fibres; it could merely mean that the cutaneous branch is more superficially placed and therefore more easily excited. However, the result is of practical importance in that it makes it possible to excite sensory fibres in isolation from motor fibres, so that conduction velocity in the two groups can be compared.

Relative Conduction Velocities of Motor and Sensory Fibres.—In three of the four subjects described in the previous section, sensory fibres in the anterior tibial nerve at the ankle were stimulated by a weak shock which was insufficient to excite motor fibres; in each case a small sensory action potential was recorded at the head of the fibula using surface electrodes. The intensity of the stimulus at the ankle was then increased until it was maximal for the motor fibres to the extensor digitorum brevis and motor latency was recorded through surface electrodes in the position shown for the pair 3 and 4 in Fig. 5. Finally, the motor fibres to the extensor digitorum brevis were stimulated at the head of the fibula through the surface electrodes used previously for recording the nerve action potential (in the position shown for electrodes 7 and 8 in Fig. 5), the stimulus again being maximal for motor fibres.

Results in the three subjects are shown in Table I. Latencies to the base and to the peak of the sensory action potential are given separately in the first two columns of the table. Motor latencies with stimulation at the ankle and at the head of the fibula are shown in the third and fourth columns of Table I and motor conduction time between the two stimulus positions is shown in the last column. In this way a direct comparison may be made between conduction times in motor and sensory fibres in the same nerve trunk, measured in both cases over the same distance between the knee and ankle. From Table I it can be seen that in all three subjects conduction time for the fastest sensory fibres (*i.e.*, latency measured to the base of the nerve action potential) was slightly shorter than motor conduction time over the same distance.

TABLE I

MOTOR AND SENSORY CONDUCTION IN THREE HEALTHY SUBJECTS

Subject	Sensory Latency (msec.)		Motor Latency (msec.)		Motor Conduction Time (msec.) Knee to Ankle
	To Base	To Peak	From Ankle	From Knee	
J.D.	5·8	6·4	3·8	10·1	6·3
R.G.	7·2	7·7	3·8	11·1	7·3
A.J.	6·6	7·2	3·8	10·8	7·0

In the case of sensory fibres, conduction time includes excitation time at the site of nerve stimulation, which is of the order of 0·1 msec. (Hunt, 1954). Motor conduction time is obtained by subtraction of one latency from another and no correction for excitation time need be made; thus the absolute differences in conduction time between motor and sensory fibres are probably slightly greater than those shown. It may be concluded that in these subjects, conduction velocity in the fastest sensory fibres of the anterior tibial nerve was slightly greater than in the fastest motor fibres to the extensor digitorum brevis.

The Range of Normal Variation.—In order to establish the range of normal variation, 39 control subjects were examined. Observations were made on a few healthy subjects working in the laboratory and also on patients of widely varying ages, all of whom were without evidence of local pathology in the leg. The clinical diagnosis in control subjects is shown in Table II from which it will be seen that four patients with lateral popliteal palsies and one with a suspected anterior tibial nerve lesion were

TABLE II

CLINICAL DIAGNOSIS IN 39 CONTROL SUBJECTS

Epilepsy	9	Carpal tunnel syndrome	2
Lateral popliteal nerve palsy	4	Cervical syringomyelia	1
Cerebral tumour	4	Gallstones	1
Cerebral vascular disease	2	Hysteria	1
Dementia	2	Anterior tibial nerve lesion	1
Migraine	3	Parkinsonism	1
Cervical spondylosis	2	Healthy subjects	4
Ulnar neuritis	2	Total	39

included; in these cases control measurements were made on the unaffected leg.

In each case the anterior tibial nerve was stimulated on the dorsum of the ankle and the action potential of the afferent volley in the lateral popliteal nerve recorded through a pair of No. 18 hypodermic needles. The lower needle was always inserted at right angles to the skin at the level of the neck of the fibula so that its tip lay 1·5 cm. from the surface immediately behind the bone. The upper needle was placed parallel to it and 3 to 4 cm. higher in the leg, its tip lying behind the tendon of biceps femoris close to its insertion into the head of the fibula.

Action potentials were recorded successfully in all 39 control subjects. In each case the growth of the nerve action potential with increasing stimulus strength was watched on the oscilloscope until a point was reached at which its amplitude appeared to remain constant. Photographic records were then made. Peak-to-peak amplitude of the potentials is shown in Fig. 6, plotted against the subject's age in years, and it can be seen that values ranged from 2 to 15·5 μv. While there appears to be some diminution in the size of the potentials in the older age groups, the scatter of the results in younger subjects is such that the difference with age is not statistically significant.

For the estimation of conduction time, latencies were measured both to the base and to the peak of the main deflection of the action potential, this deflection being due to negativity of the lower recording electrode with respect to the upper one. Although the time of arrival of impulses at the lower recording electrode is indicated by the onset (*i.e.*, the base) of the negative deflection, measurement to this point was difficult in the case of small potentials, whereas latencies to peak could be measured accurately. In the 39 control subjects peak latencies ranged from 5·3 msec. to 8·8 msec. and in spite of scatter showed an approximately linear relation to conduction distance.

When conduction distance is divided by latency an estimate of conduction velocity is obtained. Velocity calculated in this way inevitably includes certain errors; on the one hand the excitation time of the nerve will tend to reduce it, whereas any spread of current from under the stimulating cathode will tend to increase it. However, in relation to the length of nerve examined (25 to 35 cm.) these errors are small, and the estimation of velocity does at

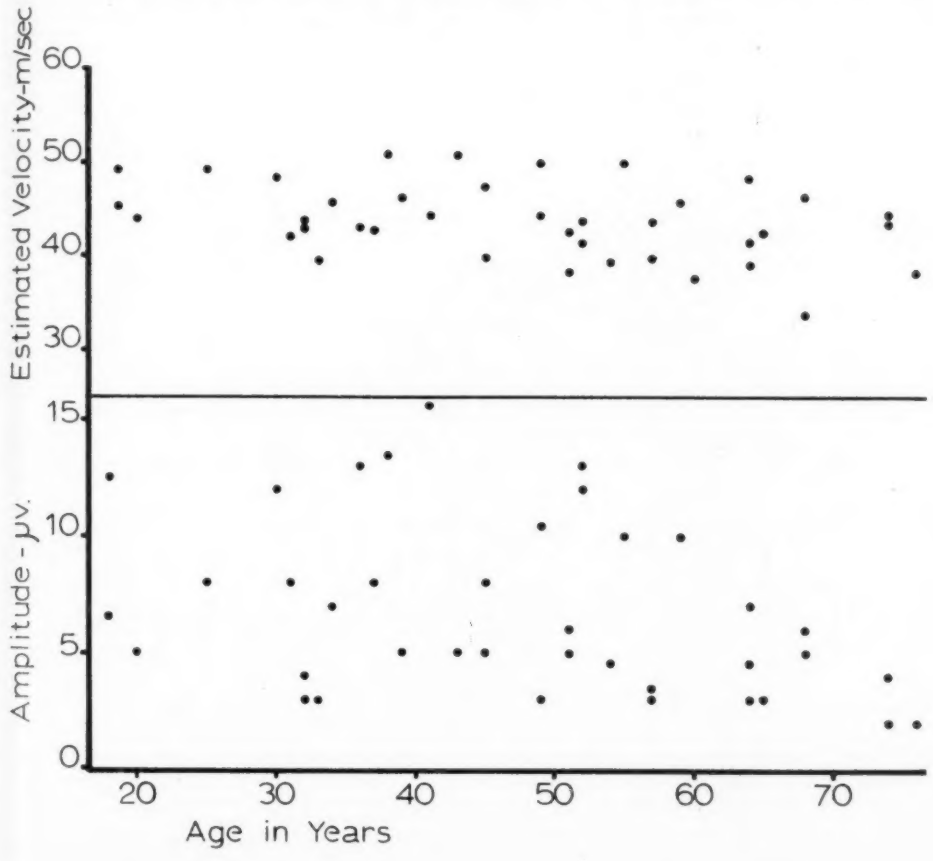

FIG. 6.—Amplitude and conduction velocity of action potentials recorded from lateral popliteal nerve plotted against age in 39 control subjects.

least provide a correction for conduction distance in different subjects provided that the same technique is used. Conduction velocity derived from peak latency in the 39 control subjects ranged from 33·8 to 51·8 m./sec. and in Fig. 6 it has been plotted against the subject's age in years. Some decrease in conduction velocity in the older age groups is apparent; there were, for example, 19 subjects over the age of 50 and 20 subjects under this age; mean velocity was 42·6 m./sec. (S.D. ±4·6) in the former, and 45·5 m./sec. (S.D. ± 3·5) in the latter group, this difference being statistically significant ($p<0.05$).

It has already been pointed out that latency measured to the base of the action potential is unreliable for small action potentials. With potentials of more than 5 μv in amplitude this difficulty does not arise, and in such cases velocities derived from base and peak measurements may be compared. There were 19 subjects in the control group with nerve action potentials greater than 5 μv in amplitude and their results are shown graphically in Fig. 7. Base velocity in the 19 subjects ranged from 47·3 m./sec. to 63·0 m./sec. (mean 53·0 m./sec., S.D. ± 3·85) whereas peak velocity ranged from 39·8 m./sec. to 51·0 m./sec. (mean 45·9 m./sec. S.D. ± 3·25). These figures may be compared with the range of 35·6 to 63·5 m./sec. (mean 49·7 m./sec., S.D. ± 7·1) given by Thomas, Sears, and Gilliatt (1959) for the maximal velocity of motor fibres to the extensor digitorum brevis in healthy subjects.

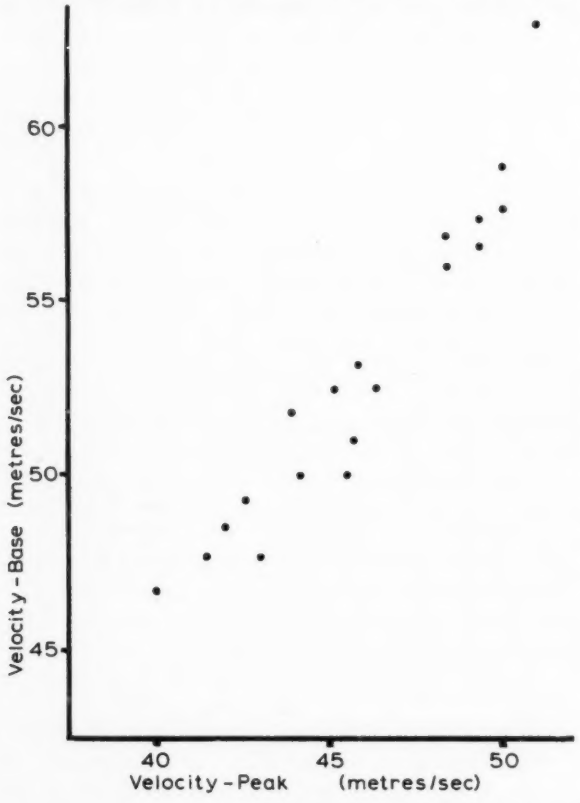

FIG. 7.—Conduction velocity calculated from latency to base of action potential plotted against velocity calculated from peak latency in 19 control subjects.

Although a triphasic waveform was seen in most of our control subjects, there were four in whom the nerve action potentials were polyphasic. Polyphasic potentials were also seen in pathological cases and they will be discussed in a later section.

Investigation of Pathological Cases.—Lateral popliteal nerve action potentials were examined in 35 patients with neurological disorders, the standard technique described for the control subjects being used in each case; the anterior tibial nerve at the ankle was stimulated with a maximal or near-maximal shock, and the nerve action potential recorded from the lateral popliteal nerve at the head of the fibula through a pair of No. 18 hypodermic needles placed 3 to 4 cm. apart as previously described. Since the pathological group contained a proportion of patients with small action potentials latency was measured to the peak of the main deflection and values for conduction velocity in subsequent sections are derived from peak latencies in all cases.

Multiple Sclerosis.—Fourteen patients with multiple sclerosis were examined. Whereas patients with spinal cord disease localized to the cervical region (cervical spondylosis, cervical syringomyelia) were included in the control group, those with multiple sclerosis were excluded on the grounds that a plaque in the lumbar cord might affect lateral popliteal nerve action potentials; actual muscle wasting as a result of denervation is known to be rare in this condition but it was felt that lesser degrees of interference with the ventral root outflow to the extensor digitorum brevis would be difficult to exclude. While this should not affect sensory impulses it might well modify the antidromic volley in motor fibres and alter its contribution to the action potential.

The ages of the 14 patients with multiple sclerosis ranged from 26 to 51 years, and in Table III the results are compared with those described previously for control subjects of similar age.

It is clear from Table III that the differences between patients and controls were negligible in respect of both amplitude and conduction velocity of the nerve action potential. Polyphasic action potentials were seen in three out of 14 patients with multiple sclerosis, and their significance is discussed in a later section.

TABLE III

LATERAL POPLITEAL NERVE ACTION POTENTIALS IN MULTIPLE SCLEROSIS

	14 M.S. Patients Aged 26-51		20 Control Subjects Aged 18-49	
	Range	Mean	Range	Mean
Conduction velocity (m./sec.)	38·5-52·8	46·3	39·8-51·0	45·5
Amplitude (μv)	3-15	7·9	3-15·5	7·6

Motor Neurone Disease.—Five patients with motor neurone disease were examined; their ages ranged from 54 to 62 years. Patients with severe wasting of the lower limbs were chosen, and in each case the response of the extensor digitorum brevis to nerve stimulation was monitored through surface electrodes placed over the expected position of the muscle, the wasting being of such severity that the muscle belly could no longer be palpated through the skin. In three patients there was no muscle response to stimulation of the anterior tibial nerve at the ankle, and in the other patients only two or three surviving motor units were activated. Although few if any motor nerve fibres were excited by the stimulus, an action potential was recorded in every case from the lateral popliteal nerve at the head of the fibula; action potential amplitude in the five patients ranged from 2·5 to 3·4 μv as shown in Table IV.

TABLE IV

NERVE ACTION POTENTIALS IN MOTOR NEURONE DISEASE

Subject	Age (years)	Conduction Velocity (m./sec.)	Amplitude (μv)
D.K.	62	33·2	2·5
M.Mc.	59	37·3	3·3
M.H.	54	41·5	3·0
D.V.	56	40·7	3·0
E.W.	60	40·5	3·4

From these observations it was concluded that when the motor fibres in the anterior tibial nerve had been virtually eliminated by disease, sensory fibres could still be excited in sufficient numbers to give rise to a recordable action potential.

When the conduction velocities shown in Table IV are compared with those of control subjects over the age of 50 years it is clear that conduction was generally slower in the patients with motor neurone disease. These patients were severely paralysed and their reduced conduction velocities were almost certainly due to the low limb temperature which we were unable to correct by simple measures.

Peripheral Neuritis and Subacute Combined Degeneration of the Spinal Cord.—In contrast to the patients with spinal cord disease, those with peripheral neuritis and subacute combined degeneration showed marked changes in the nerve action potential. Three patients with chronic peripheral neuritis were examined (Table V), in each case muscular weakness in the legs was accompanied by loss of knee and ankle jerks and impairment of superficial sensation on the feet. In none of these three patients was it possible to record a nerve action potential even when using a stimulus to the anterior tibial nerve of considerably higher voltage than that which would be tolerated by a healthy subject.

TABLE V

NERVE ACTION POTENTIALS IN PERIPHERAL NEURITIS, SUBACUTE COMBINED DEGENERATION, HEREDITARY ATAXIA, AND PERONEAL MUSCULAR ATROPHY

Subject	Diagnosis	Age (years)	Action Potential Amplitude (μv)	Conduction Velocity (m./sec.)
E.A.	Polyneuritis (unknown aetiology)	52	Absent	—
S.K.	Diabetic neuritis	52	Absent	—
J.J.	Diabetic neuritis	36	Absent	—
E.M.	Subacute combined degeneration	63	Absent	—
P.P.	" " "	51	1	29
I.W.	" " "	42	<1	45
H.W.	" " "	67	3·5	46
W.B.	Hereditary ataxia	31	Absent	—
A.E.	Peroneal muscular atrophy	33	Absent	—
D.C.	" " "	54	4·0	41·5
B.G.	" " "	53	2·5	37

It can be seen from Table V that in four patients with subacute combined degeneration the results were more variable; in the case of E.M. the action potential was absent altogether and in P.P. and I.W. minimal deflections of the trace were seen (marked by arrows in Fig. 8 a and b respectively). It may be noted that whereas the minimal deflection shown in Fig. 8b had a normal latency, that shown in Fig. 8a was obviously delayed (latency to peak 11·5 msec.), from which conduction velocity was estimated to be 29 m./sec. In the fourth patient (H.W.) a triphasic potential of normal latency was recorded (Fig. 8c). It is interesting that in the three patients with much diminished or absent action potentials clinical examination showed mainly a picture of peripheral nerve involvement with flexor plantar responses and superficial sensory loss of stocking distribution. In the fourth patient (H.W.) there was evidence of spinal cord involvement with extensor plantar responses and with preservation of superficial sensation in spite of gross impairment of joint sense.

Hereditary Ataxia and Peroneal Muscular Atrophy.—In one patient with hereditary ataxia (W.B.), a pyramidal and cerebellar syndrome was accompanied by pes cavus, scoliosis, and cardiac

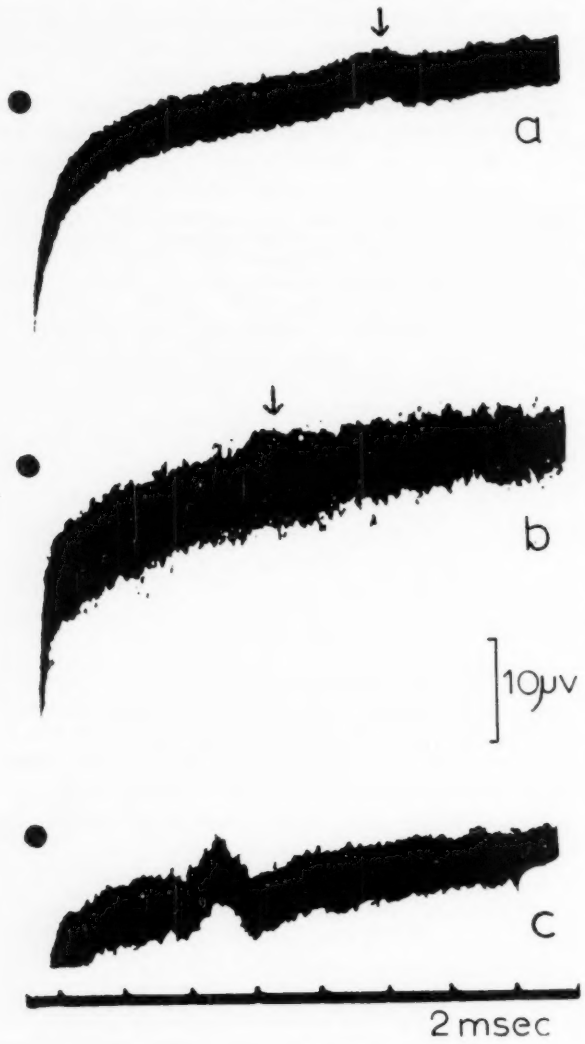

FIG. 8.—Action potentials recorded from the lateral popliteal nerve in three patients with subacute combined degeneration. Stimulus at mark. One hundred faint traces superimposed.

changes. In this patient some wasting of the leg muscles was present with impairment of both deep and superficial sensation in the feet, and it can be seen from Table V that the lateral popliteal nerve action potential was absent.

Three patients with classical peroneal muscular atrophy (Charcot-Marie-Tooth disease) were examined. In A.E. the only sensory abnormality on clinical testing was some loss of vibration sense in the feet but the lateral popliteal nerve action potential was absent. In D.C. superficial sensation was preserved but there was mild impairment of both vibration and joint sensation in the feet. In B.G. appreciation of vibration and joint sensation was intact, the only clinical sensory abnormality being mild subjective blunting of pin-prick on the toes compared with the shins. In both D.C. and B.G. low-voltage polyphasic potentials were recorded.

Lateral Popliteal (Peroneal) Nerve Palsy.—Four patients with unilateral foot-drop of acute onset were seen. One patient first noticed his symptoms on recovering from a general anaesthetic after an abdominal operation; a second patient developed foot-drop after a particularly vigorous game of football. In the other two cases there was no definite history of trauma, but in each of them the onset was abrupt, the patient suddenly becoming aware of weakness of the ankle and numbness of the dorsum of the foot. The patients were examined between four and 12 weeks after the onset, by which time all reported improvement compared with their initial condition. No wasting of the anterior tibial or peroneal muscles was noted but weakness was still present in every case. There were mild sensory changes over the dorsum of the foot and toes in all four patients, subjective diminution to pin-prick and cotton wool being present without complete loss of either modality. In two patients the peroneal nerve on the affected side was considered to be thickened in the region of the neck of the fibula. The nervous system was otherwise normal in every case.

Results are shown in Table VI, from which it can be seen that there was diminution in action potential amplitude with slowing of conduction velocity on the affected side in all four patients.

A typical result from one of the four patients is shown in Fig. 9. The patient, a clerical worker aged 31, suddenly found when walking to work one morning that his right foot 'flapped' when he put it to the ground; shortly afterwards he noticed an abnormal sensation on touching the skin on the dorsum of the ankle and foot. At the time of the first examination one month after the onset, the patient was already recovering and the only abnormality present on formal neurological examination was mild weakness of the anterior tibial and peroneal muscles on the right, with hypalgesia to pin-prick restricted to the dorsum of the foot and toes. When the right extensor digitorum brevis was sampled with a concentric needle electrode no denervation potentials were seen and the number of motor units under voluntary control was not obviously reduced. With the concentric needle electrode *in situ*, the anterior tibial nerve was stimulated on the dorsum of the ankle, a muscle action potential of normal latency being recorded (Fig. 9a). When the motor fibres were stimulated at the neck of the fibula the latency of the muscle response was again normal (Fig. 9c), conduction velocity for the fastest fibres between the two stimulus levels being 48·5 m./sec.

TABLE VI

NERVE ACTION POTENTIALS IN LATERAL POPLITEAL (PERONEAL) PALSY

Subject	Age	Affected Leg		Unaffected Leg	
		Amplitude (μv)	Conduction Velocity (m./sec.)	Amplitude (μv)	Conduction Velocity (m./sec.)
C.C.	31	*a 3·0 b 5·0 c 6·2	a 33·2 b 38·8 c 41·5	8·0	42·0
B.D.	45	2·0	36·7	8·0	39·8
W.P.	68	3·1	33·5	5·8	46·3
G.W.	20	3·0	42·5	8·5	47·5

*Time interval a to b, four months; b to c, five months.

When this procedure was repeated on the unaffected leg latencies were almost identical (Figs. 9b and 9d), motor conduction velocity being 46·3 m./sec. However, when the anterior tibial nerve was stimulated on the dorsum of the ankle with recording needles in the standard position at the head of the fibula, the amplitude of the nerve action potential on the right was much reduced and could not be increased by raising stimulus intensity. In addition the normal triphasic waveform was lost and latency to peak increased (Fig. 9e). For comparison the normal nerve action potential recorded from the unaffected leg is shown in Fig. 9f.

A follow-up examination was carried out four months later when the patient appeared to have made a complete clinical recovery. Substantial recovery of the nerve action potential had also occurred (C.C., b, in Table VI) but its amplitude remained less than on the control side. A third examination nine months after the onset showed a further slight increase in the amplitude of the action potential (C.C., c, in Table VI).

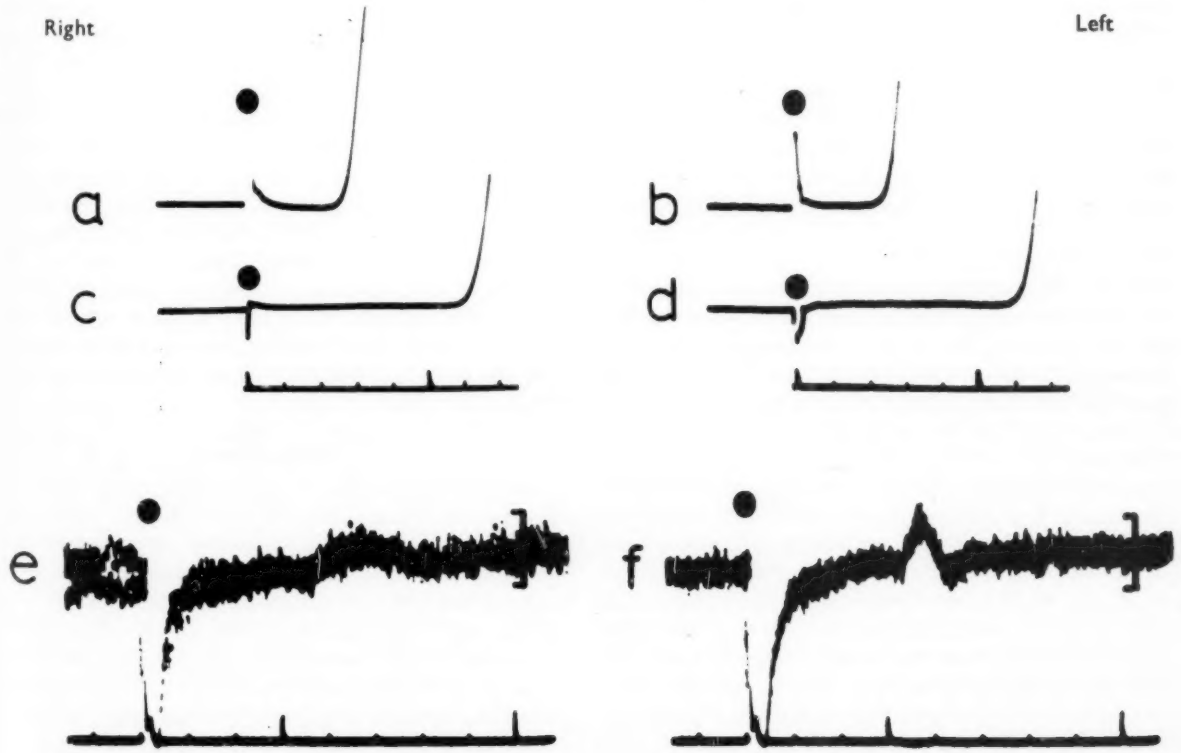

FIG. 9.—Subject C.C. Right lateral popliteal nerve lesion. Onset of muscle action potentials recorded from the extensor digitorum brevis in response to motor nerve stimulation at ankle (a and b), and at head of fibula (c and d), to show similar motor latencies on the two sides. Nerve action potentials recorded from lateral popliteal nerve at head of fibula with stimulation at ankle (e and f) show markedly reduced amplitude on affected side. Stimulus at mark and time interval 2 and 10 msec. throughout. Five traces superimposed and calibration 10 μv for e and f only.

This case is described in detail to show that with a mild lateral popliteal nerve lesion marked changes in the nerve action potential may occur without any abnormality in motor conduction velocity as estimated from the latencies of the fastest fibres.

Significance of Polyphasic Potentials.—Polyphasic potentials were seen in four control subjects, three patients with multiple sclerosis, and two patients with peroneal muscular atrophy. In each of them the main deflection of the action potential was still recognizable but this was followed by waves of lower amplitude lasting for 2 to 4 msec. The investigation of polyphasic potentials was made difficult by the small amplitude of the late components which was less than the amplifier noise level and usually of the order of 0·5 to 1·0 μv. For this reason departures from normal waveform were not apparent until superimposed records were examined, and some doubt arose as to whether or not the late waves were artefacts arising in the recording system.

In one patient, however, it was possible to investigate the phenomenon further by moving the stimulating cathode proximally along the course of the anterior tibial nerve for a sufficient distance to show that the late waves were propagated with a reduced velocity.

The patient, a taxi-driver aged 36 years, first noticed numbness in the territory of the anterior tibial nerve after falling asleep with his legs on a chair, from which it was suspected that he might have sustained a mild pressure lesion of the anterior tibial nerve at the ankle by sleeping with one foot crossed on top of the other. Except for diminished superficial sensation on the dorsum of the foot and toes, no abnormality could be detected on clinical examination, and the patch of numbness was already fading at the time of the electrical investigation. However, a prolonged polyphasic action potential of low voltage was recorded from the lateral popliteal nerve on the affected side whereas a normal triphasic action potential, 5 μv in amplitude, was recorded from the opposite leg. In the records shown in Fig. 10 the nerve action potential was recorded from a single steel needle behind the head of the fibula of the affected leg against an indifferent electrode on the outer surface of the thigh. The stimulus was first applied to the anterior tibial nerve on the dorsum of the ankle slightly below the intermalleolar line (Fig. 10a), after which the stimulating cathode was moved proximally for 5 cm. (Fig. 10b). Comparison of the two traces makes it clear that the late oscillations present are true propagated potentials, latency measurements to early and late components indicating conduction velocities as different as 45 and 26 m./sec. respectively.

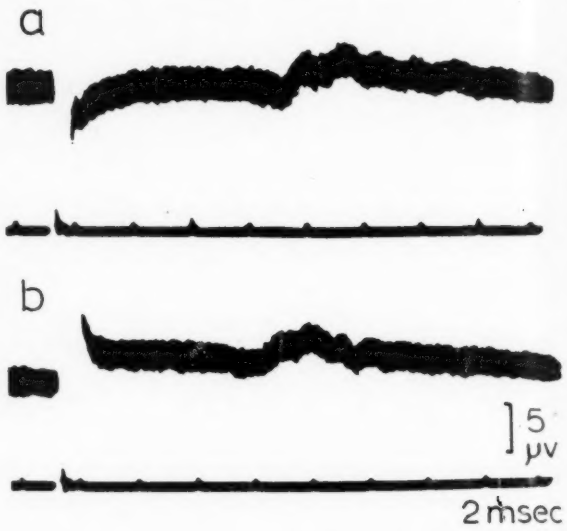

FIG. 10.—Action potentials recorded from the lateral popliteal nerve in a patient (J.B.) with a suspected anterior tibial nerve lesion. Stimulating cathode over anterior tibial nerve was moved 5 cm. proximally between (a) and (b). Recording electrodes unchanged throughout. Records show stimulus artefact followed by low voltage polyphasic action potential in each case. One hundred faint traces superimposed.

With stimulation of the posterior tibial nerve and surface recording in the popliteal fossa, Buller (1959) was able to demonstrate differential velocities of early and late components of the medial popliteal nerve action potential in healthy subjects. His results, together with our own findings in the patient cited above, suggest that the late components recorded in our other cases may also have been due to activity in slowly conducting fibres. However, their investigation clearly requires apparatus with a higher signal-to-noise ratio than that used in the present work. This should prove to be a problem of great interest when suitable recording apparatus becomes available.

Discussion

In the upper limbs it is possible to stimulate the fingers and record an action potential from the median or ulnar nerves at the wrist (Dawson, 1956). Alternatively it is possible to stimulate at the wrist and record nerve action potentials at a higher level in the arm (Dawson and Scott, 1949). In patients with neurological disorders, these techniques have already proved to be of considerable practical value, and the present investigation is an attempt to extend them to the nerves of the lower limbs. We have not succeeded in recording action potentials from the anterior or posterior tibial nerves at the ankle with stimulation of the digital nerves in the toes, and have concentrated upon recording from the lateral

popliteal nerve at the head of the fibula with stimulation of the anterior tibial nerve at the ankle. At both levels the nerve fibres are superficial and are easily located through the skin so that stimulating and recording electrodes can be accurately placed. In this respect the lateral popliteal is a more convenient nerve to examine than the medial popliteal which lies deeply in the popliteal fossa, and we have not attempted to record from the latter. However, Buller (1959) has already done this successfully in healthy subjects using a storage tube, and this presents a promising field for further investigation.

In spite of the superficial position of the lateral popliteal nerve, it became clear at the start of the present work that the action potentials we were attempting to record were very much smaller than those recorded previously from the median and ulnar nerves in the arm. Even when surface electrodes were replaced by needles inserted close to the lateral popliteal nerve, the potentials did not exceed 15 μv in amplitude, which may be compared with the range of 33 to 117 μv reported for the ulnar nerve in the forearm by Gilliatt and Thomas (1960). However, the technical difficulties of recording small potentials need not be exaggerated. Provided that muscular relaxation is adequate, potentials with an amplitude substantially less than the amplifier noise level can be recorded successfully by photographic superimposition of a number of faint traces, and in our 39 control subjects there was no instance in which we failed to record a potential from the lateral popliteal nerve.

The anterior tibial nerve at the ankle contains motor fibres to the extensor digitorum brevis as well as sensory fibres from the dorsum of the foot, and a stimulus in this situation may thus be expected to excite both groups of fibres. In attempting to analyse the extent to which impulses in sensory fibres contribute to the mixed nerve action potential, we have been helped by the fact that patients with motor neurone disease commonly show complete loss of motor fibres to the extensor digitorum brevis with preservation of sensation. From our observations on these patients it is clear that sensory fibres are present in the anterior tibial nerve in sufficient numbers to produce a recordable action potential when all the motor fibres have been eliminated by disease. Unfortunately, we have not been able to demonstrate the contribution of motor fibres in a similar way. For this purpose one would need to examine patients with sensory loss but with full preservation of motor innervation. In his work on the arm, Dawson (1956) was able to study a patient with sensory radicular neuropathy (Case 3 of Ogden, Robert, and Carmichael, 1959); in this patient a nerve action potential with an amplitude of 28 μv was recorded from the ulnar nerve above the elbow which was considered to be derived entirely from antidromic impulses set up in motor fibres at the wrist. Recordings from the lateral popliteal nerve in patients with sensory radicular neuropathy have not been carried out, and in the absence of such information the proportion of the action potential which is due to impulses in motor fibres remains uncertain.

These considerations are important in the interpretation of findings from pathological cases. A small action potential with an amplitude below the lower limit of the normal range could be due to a partial lesion of both motor and sensory fibres or to a complete lesion of one with preservation of the other. Thus it is only when the nerve action potential is wholly absent that one may conclude that both motor and sensory fibres are affected. In the present series the nerve action potential has been wholly absent in all the patients with polyneuritis and in a proportion of those with subacute combined degeneration and hereditary disorders such as peroneal muscular atrophy. From the clinical point of view, therefore, these conditions seem to offer the most promising field for further investigation and a study of diabetic neuritis is now being undertaken (Gilliatt and Willison, 1962).

At this point it may be asked what is the nature of the nerve lesion causing diminution or loss of the action potential. Degeneration of some or all of nerve fibres would be expected to have this result but in our patients with pressure palsies of the lateral popliteal nerve recovery was so rapid that degeneration cannot have occurred, and yet abnormalities of the action potential were consistently present. The results in these patients suggest that dispersion of the ascending volley may be an important factor. For example, in the case illustrated in Fig. 9 conduction velocity in the fastest motor fibres to the extensor digitorum brevis was normal, although the nerve action potential was much reduced in size and showed an increased latency to peak. This result is similar to our previous findings in patients with ulnar nerve lesions at the elbow and it is most easily explained by dispersion of impulses in different fibres of the nerve. For this reason the nerve action potential is a more sensitive index of disturbed function than the simple measurement of conduction time for the fastest surviving motor fibres.

Finally, it must be emphasized that the recording of nerve action potentials only provides information about motor fibres and about the larger and more rapidly conducting sensory fibres. For the small afferent fibres there is no satisfactory technique which can be applied to patients at the present time. However, the presence of degeneration in small

fibres can be inferred from the results of histamine or cold vasodilatation tests (Bonney, 1954), and these techniques can sometimes be of great value in supplementing nerve conduction studies (Bonney and Gilliatt, 1958).

Summary

When the anterior tibial nerve at the ankle was stimulated with single shocks, it proved possible to record the action potential of the ascending volley from the lateral popliteal nerve at the head of the fibula. Surface and needle recording electrodes were tried, and it was concluded that subcutaneous needles inserted close to the nerve trunk were more satisfactory than surface electrodes placed on the skin over the course of the nerve.

Action potentials were recorded from the lateral popliteal nerve in 39 control subjects; their amplitude varied from 2·0 to 15·5 μv, the lowest values being seen in elderly subjects. The conduction velocity of the ascending volley was also slightly reduced in the older subjects.

Results in patients with multiple sclerosis did not differ significantly from those of the control group, and in patients with motor neurone disease it was possible to record nerve action potentials even when the motor fibres of the anterior tibial nerve had been eliminated by the disease.

In contrast to the patients with spinal cord disease, nerve action potentials were absent or grossly abnormal in those with polyneuritis or localized lesions of the lateral popliteal nerve. Abnormalities of the action potential were also present in patients with subacute combined degeneration and with peroneal muscular atrophy, but the results were more variable than in polyneuritis.

We wish to thank members of the staff of the National Hospital and of the Middlesex Hospital who have referred patients for investigation.

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A SYNDROME OF CONTINUOUS MUSCLE-FIBRE ACTIVITY

BY

HYAM ISAACS*

Johannesburg

The purpose of this paper is to describe two cases of a hitherto unknown syndrome superficially resembling myotonia. Detailed studies have helped to separate this syndrome of continuous muscle-fibre activity from a group of 100 myotonic subjects, and it will be referred to in this paper as the 'syndrome of continuous muscle-fibre activity'. This descriptive label has been chosen, though the more imaginative may favour 'armadillo disease', a name by which these cases are likened to the slow moving, armour-plated quadruped.

Case Reports

Case 1.—M.P., aged 12, was referred for investigation with a complaint of stiffness of the muscles which had been progressive over the past three years. The patient (Fig. 1), according to his parents, was reasonably normal up to the age of 9 years, quite able to run about and compete with his friends. They stated, however, that from the age of 5 years he had some difficulty in walking and for the past three years he had been severely incapacitated by increasing muscle stiffness, present night and day. The stiffness was increased by voluntary muscle contraction, particularly obvious after the third and fourth movements after which the condition improved and he was able to use his limbs more freely for a time, before they stiffened up again despite continued movement. At times he has had the greatest difficulty with the initial movements and occasionally complained of stiffness of the jaw and tongue while eating and talking. His speech had not been affected but he had at times experienced difficulty in breathing due to stiffness of the chest. Defaecation and micturition were normal. He sweated a great deal and always felt warm. There was no family history of muscle disease; his parents were alive and well and showed no evidence of myopathy. His past illnesses included measles and chickenpox, from which he recovered in the usual time without complications and which were not related to the onset of the present difficulties.

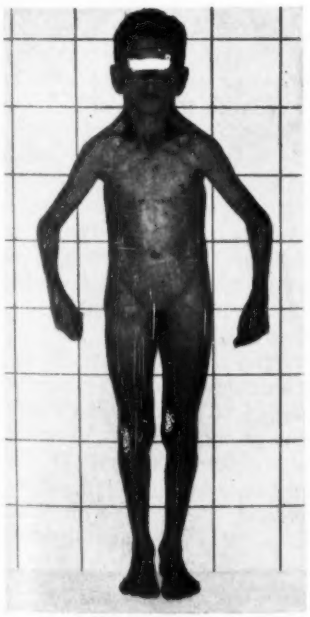

FIG. 1.—Note stiff posture and contraction of muscles (Case 1); contraction of trapezius is not be be mistaken for webbing.

On examination, the patient was found to be underweight and undersized for his 12 years, his height being 48 in., span 47 in., and weight 45 lb. Pulse rate was 124/minute, blood pressure 120/80 mm. Hg. The heart was normal. The abdominal wall was extremely tense but no hepatosplenomegaly or masses were felt. The genitalia were small, the testes pea-sized and soft. The child was intellectually and emotionally normal. Tendon reflexes were impossible to elicit, but the plantar response was normal. Motor power was generally poor. The cranial nerves were intact. Sensation and coordination seemed normal. His posture was stiff and all muscles were in a state of persistent contraction. The chest moved poorly with respiration; there was hardly any subcutaneous tissue; the muscles were well-defined and firm.

All muscles showed evidence of fasciculation and were weaker than normal. The weakness affected particularly the extensor muscles of the forearms, arms, extensor and peroneal muscles of the legs, and the small muscles of the hands and feet. He walked with extreme difficulty in a rigid manner. The degree of stiffness was more marked in the distal than proximal muscles, being unaffected by the warmth of summer or the cold of winter. The patient was constantly covered by a thin film of perspiration and had a persistent tachycardia of 120/minute with the body temperature averaging 99°F. The upper limbs could only be fully extended passively and then with difficulty as it appeared that some degree of contracture had occurred. Passive extension was quite painless.

Radiographs of the skull, chest, and spine revealed no

*201 Lister Buildings, 276 Bree Street, Johannesburg.

TABLE I

RESULTS OF LABORATORY INVESTIGATIONS

	Case 1	Case 2
Haemoglobin (g. %)	14·8	14·7
Leucocytes (thousands/c. mm.)	6·7	7·2
Neutrophils (%)	57	65
Eosinophils (%)	2·0	1%
Basophils (%)	1·0	0
Monocytes (%)	4·0	6
Lymphocytes (%)	36·0	28
Bone marrow	Normal cellularity	Normal cellularity
Erythrocyte sedimentation rate (mm./hr.)	4	1
Wassermann reaction	Negative	Negative
Fasting blood sugar (mg./100 ml.)	97	120
Blood urea (mg./100 ml.)	17	36
Thymol flocculation	Negative	Negative
Thymol turbidity (units)	2	1·5
Colloidal red test	Negative	+
Takata Ara reaction	Negative	Negative
Cephalin cholesterol flocculation (24-hour reading)	Negative	Negative
Alkaline phosphatase (King-Armstrong units)	10	7·6
Serum		
Bilirubin total (mg./100 ml.)	0·4	0·4
Proteins (g./100 ml.)	6·5	6·9
Albumin (g./100 ml.)	4·2	3·4
Globulin (g./100 ml.)	2·3	3·5
γ Globulin	0·72	1·21
Cholinesterases % of normal activity	100	90
Iron (μg./100 ml.)	100	100
Co_2 content (mEq./litre)	21·0	23·0
Potassium	3·6	4·4
G.O. transaminase units (normal, 34-107)	60	70
G.P. transaminase units (normal, 13-95)	65	85
Sodium (mEq./litre)	138	139
Chloride (mEq./litre)	101	102
Amylase (Street-close units)	35	27
Calcium (mEq./litre)	4·9	4·6
Magnesium (mEq./litre)	1·7	1·2
Creatinine (mg./100 ml.)	1·0	1·2
Cholesterol (mg./100 ml.)	150	207
Total lipids (mg./100 ml.)	451	451

	Case 1	Case 2
Serum—continued		
Protein-bound iodine (μg./100 ml.)	4·3	3·3
Plasma inorganic phosphorus (mg./100 ml.)	3·6	4·8
Urine analysis		
Sodium (mEq./litre)	152	156
Potassium (mEq./litre)	27	88
Chlorides (mEq./litre)	156	148
Calcium (mg./litre)	81	110
Phosphorus (mg./litre)	672	900
Creatinine (mg./litre)	1,040	2,664
Creatine	500	216
24 hr. volume average (ml.)	700	1,080
17-Ketosteroids (as dehydroisoandrosterone) (mg./24 hr.)	5·5	8·3
17-Hydroxycorticosteroids (P.S.C.)	4·0	8·7
Total 17-hydroxycorticosteroids	7·3	14·8
F.S.H. 24 hr. (mouse units)	6	6-12
Porphyrin excretion	Normal	Normal
AS and Pb excretion	Normal	Normal
Insulin sensitivity test	Normal	Normal
Glucose tolerance test	Normal	Normal
Cerebrospinal fluid		
Pressure (mm. H_2O)	120	130
Cells	Nil	Nil
Protein (mg./100 ml.)	20	21
Sugar (mg./100 ml.)	80	67
Chloride (mg./100 ml.)	700	727
Lange's colloidal gold test	Negative	Negative
Basal metabolic rate under sedation	+74 +84 +68	+65
O_2 consumption (ml./min.)	240	360
Electroencephalogram	Normal	Normal
Chromatographic analysis of urine	Normal	Normal
C- reactive protein	Absent	Absent
Mucoprotein (mg./100 ml.)	102	110
Chromosomal pattern	Male	Male

abnormality. Electrocardiograms appeared normal but were difficult to interpret because of the interference from the contracting muscles. The metabolic studies are listed in Table I.

A kymographic recording of the rate of contraction of the muscles of the hand and forearm is shown in Fig. 2. Electromyography carried out with concentric needle electrodes recorded a state of constant rapid dysrhythmic discharge of independent muscle fibres (Fig. 3). The spontaneous activity was increased by voluntary contraction, an increase which peristed for $\pm$ 30 seconds after this stimulus had ceased. This period was followed by a curious period of reduced activity lasting for $\pm$ 10 seconds. This relatively silent period could be interrupted at any stage by further voluntary effort. The electrical response to percussion was normal and did not aggravate the discharge. Electrical stimulation of the nerve, as with voluntary contraction, aggravated the condition. The spontaneous discharge persisted despite local nerve block, but disappeared locally after infiltrating the muscles with procaine. General anaesthesia with pentothal had no effect, but blocking and depolarization of the motor end-plate with curare and succinylcholine abolished the spontaneous discharge and the muscle relaxed.

Several muscle biopsy specimens were obtained from proxymal and distal muscles (Fig. 4) which revealed a slight degree of variation in fibre size together with some proliferation of sarcolemmal nuclei, which tended to occur in chains, especially in relation to some of the small fibres. Most of the nuclei were dark and in some places formed small knots. There was a doubtful increase in endomysal collagen and fat.

No improvement occurred following upon the administration of quinidine, procaine amide, cortisone, or potassium depletion by exchange resins. Each of these was given for periods of at least a month in doses pushed to the point of maximum tolerance. A short-lived improvement followed injections of Dimercaprol.

Progress.—Over the next two years the patient was further investigated during the school holidays whenever possible. His condition appeared static; splints were made and applied at night to prevent flexion deformities at the elbows and wrists and to counteract the developing pes cavus. Growth remained retarded, muscle bulk had diminished, and he had several brief attacks of acute respiratory embarrassment due to chest and diaphragmatic stiffness.

After the successful treatment of Case 2 this patient was again admitted to hospital and treated in a similar fashion with dramatic results.

FIG. 2.—Kymographic tracings with the drum rotating from left to right, demonstrating the slow voluntary contraction and relaxation of the forearm muscles in the act of making a fist.

FIG. 3.—In normal muscle there is no electrical activity at rest. Note continuous dysrhythmic discharge of single muscle fibres at rest.

FIG. 4.—Muscle biopsy from left deltoid showing variations in fibre size, clumping of dark staining nuclei, row of sercolemmal nuclei, and atrophic fibres.

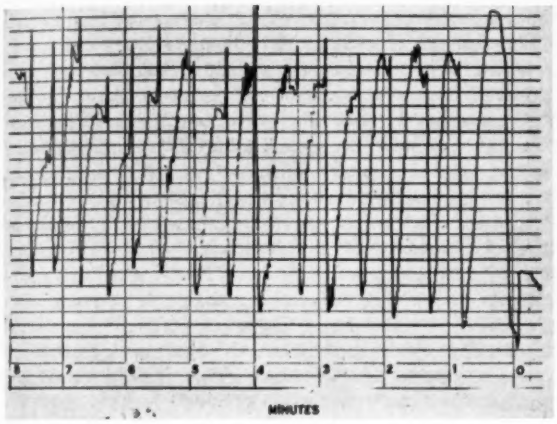

FIG. 2

FIG. 4

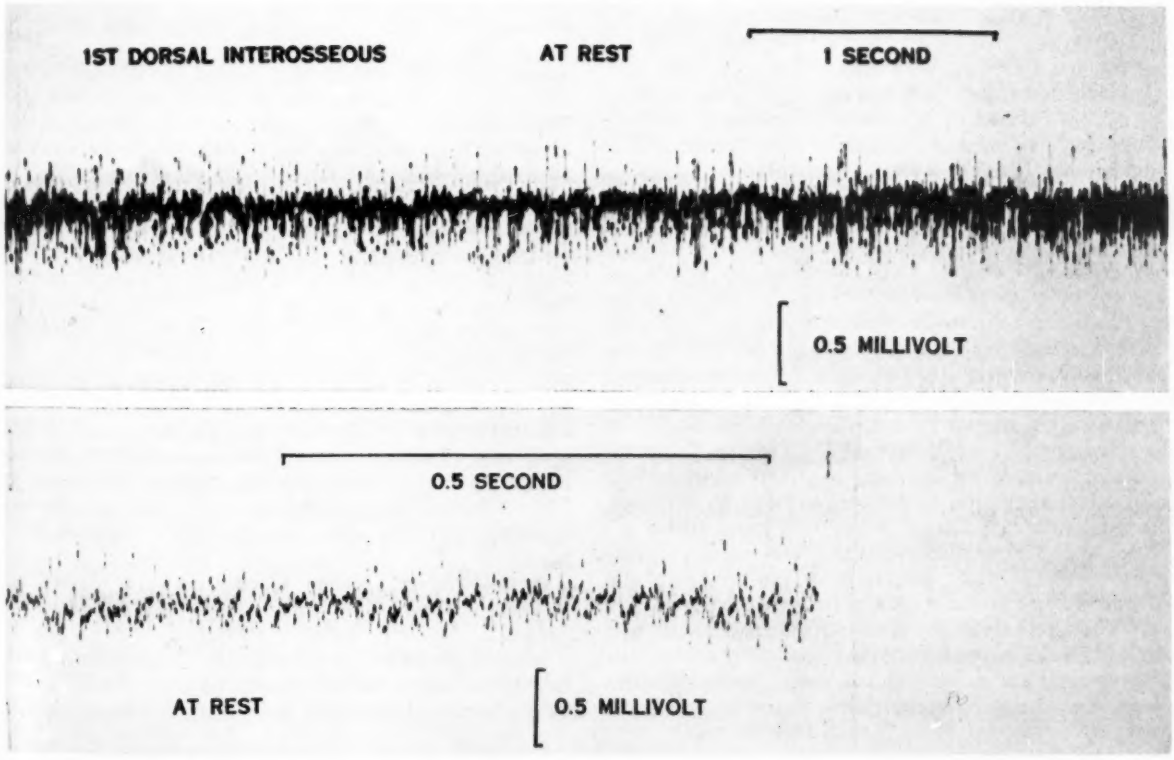

FIG. 3

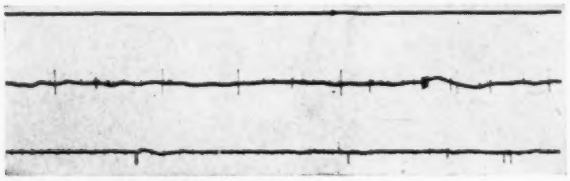

FIG. 5.—A three-channel simultaneous electromyographic recording of first dorsal interosseous (top), extensor communis (middle), and flexor profundus (bottom) muscles at rest, showing marked reduction in activity after three days' therapy in Case 1.

The patient's movement is now quite free and his muscle strength improves daily, aided by intensive physiotherapy. The temperature remains normal, the B.M.R. has fallen to the normal level of + 5 and the oxygen consumption is now 160 ml./minute. Electromyography at rest (see Fig. 3) and on effort has largely returned to normal. For the first time in four years the patient has obtained relief.

Case 2.—Mr. V.C., a butcher by trade, aged 53 years, was referred for investigation complaining of increasing stiffness of muscles over the previous six months. Up to this time he had been in perfect health. The stiffness began in the feet, spreading to the legs and later involved the arms, hands, and abdominal musculature. He noticed a hoarseness in his voice and stiffness of his tongue over this period. Associated with the stiffness there was a generalized weakness of all muscles. He had also noticed twitching in the muscles over the previous three months. He had had no difficulty with vision. Swallowing was occasionally difficult and at times the chest had become very stiff, leading to respiratory embarrassment on two occasions. The stiffness of the muscles first increased with effort, then improved with repetitive movements. He could then walk a short distance interrupted by occasional stiffening of muscles, paradoxically relieved by resting for a few seconds. The condition was growing worse. He lost 60 lb. in weight in six months.

There was no family history of muscle disorder and his five children were all well. The patient had recovered without complications from the common childhood illnesses and had remained well all his life. He had in the past consumed up to two bottles of brandy per week over a period of eight years, but had stopped drinking for the past three years. He complained of persistent sweating. The muscle stiffness was painless.

Examination revealed a middle-aged male with firm musculature which was in a state of continuous contraction. Fasciculation was noticeable in most muscles. The pulse was 100/minute, blood pressure 110/76 mm. Hg. The temperature fluctuated between 98·4 and 99·4°F.

The respiratory, cardiovascular, and genito-urinary systems were normal. Palpation of the abdomen was difficult because of the muscle activity but there was no gross enlargement of the liver or spleen or abnormal masses. Rectal examination was negative.

The cranial nerves were intact, strenuous eye closure produced difficulty in opening the eyes, most noticeable after the second and third closure. All modalities of sensation were normal. Coordination was normal. The muscles were in a state of constant contraction. Power was reduced in all muscles and in particular the extensor muscles of the forearm. Tendon reflexes were impossible to elicit, the plantar response was flexor. There was no myotonic response to percussion of the muscles including the tongue.

Special investigations as in Case 1 were essentially negative (see Table I), including barium studies of the gastrointestinal tract, an air encephalogram, and electroencephalography. The electromyographic studies were identical to those of Case 1. The patient was anaesthetized with thiopentone 500 mg. in a 5% solution and maintained on oxygen and nitrous oxide. There was no change in muscle activity during this procedure. Succinylcholine in a dose of 500 mg. produced diminution and disappearance of all electrical activity within three minutes, lasting for 10 minutes. Curare in a total dose of 10 mg. produced electrical silence after five minutes, lasting for a period of 40 minutes even though breathing began after a period of 30 minutes. During this stage irritation of the muscle or movement of the limb failed to produce electrical activity. On a separate occasion a brachial block was performed using 25 ml. of 1% xylocaine; although the arm was paralysed and anaesthetic, the motor activity persisted. This brachial block confirmed the findings of previous ulnar and median blocks which affected only the motor supply to the small muscle of the hand.

It was decided to determine the sensitivity of the motor-end plate to curare. The purpose of this test was two-fold in that it might add further information to the final elucidation of the abnormality and, secondly, might provide a therapeutic tool. The patient was prepared as for a general anaesthetic and then given 1 mg. of curare intravenously; three minutes later he complained of generalized weakness which persisted for 10 minutes. A further 1 mg. curare was then given and two minutes later he began to have difficulty with breathing and swallowing, breathing becoming rapid and shallow. There was marked generalized weakness which completely overshadowed the reduction in the state of persistent muscle activity. Curare was therefore useless therapeutically, owing to the marked sensitivity at the motor end-plate to this blocking agent. Prostigmine was given to overcome the block but response was slow and even after 15 mg. had been given intravenously slight generalized weakness persisted for the next hour. On another occasion, the patient was resistent to 1·5 mg. of decamethonium but developed generalized weakness after an additional 1·0 mg. had been given intravenously, which was not altered by 20 mg. of edrophonium. The weakness was assessed by the ulnar nerve stimulatory method described by Churchill-Davidson and Richardson (1952) and showed a normal response with perhaps slightly resistant end-plates.

Several muscle biopsy specimens were taken and revealed a similar histopathological picture to those of Case 1.

Arterial perfusions of the muscles of the forearm were carried out; there did not seem to be any increase in sensitivity to acetylcholine or potassium, but owing to the

continuous spontaneous activity the results were difficult to interpret. There was, however, increased activity following on injection of both substances given in doses which would evoke contractions in normal subjects. Calcium and magnesium infusions produced some decrease in activity but this was associated with marked muscle weakness. The discharge was unaffected by atropine, quinine, cortisone, artane, adenosine triophosphate, thiamine diphosphate, or procaine amide.

Progress.—The condition steadily deteriorated over the next year, so that the patient became unable to walk and began developing contractures in the upper and lower limbs, producing flexion deformities at the elbows and wrists and per cavus respectively. There were several episodes of respiratory embarrassment and dysphagia.

After having exhausted the possibilities of deficient or excessive ions concerned in the maintenance of normal neuromuscular response, and having abandoned both blocking and depolarising agents as therapeutic tools owing to the occurrence of severe muscle weakness, sodium hydantoinate was used in an attempt to diminish the bizarre uncontrolled discharge from the lower motor neurone which characterizes this condition. The initial dose given was 100 mg. four hourly. A marked improvement occurred over the next two days and the drug was then reduced to a maintenance dose of 100 mg. six hourly. Six months later he was quite mobile and has been able to go back to his trade. The electromyography is vastly improved both at rest and on voluntary effort, the B.M.R. was + 7, and the oxygen consumption had fallen to 280 ml./minute after two weeks' therapy.

Discussion

There are a few pathological conditions which merit comment in that they have one or two features in common with this syndrome of continuous muscle-fibre activity. The similarities, however, are at the best only superficial.

Wechsler and Brock (1922) described a myostatic variant of dystonia musculorum deformans. In this disease, however, the myostatic manifestations were 'part of the disorder and always co-exists with the kinetic disturbance of which it is only a complement'. The postures assumed, muscle tone, and other manifestations of central nervous disorder bear no similarity to the cases with continuous muscle-fibre activity. Furthermore, as pointed out by Ramsay Hunt (quoted by Wechsler and Brock, 1922) this myostatic variety of torsion dystonia should be considered in the same light as paralysis agitans with tremor on the one hand and rigidity on the other.

McArdle (1951) described the case of a young adult male who complained of weakness, stiffness, and painful muscles after exercise. The muscles were of normal size and consistency at rest, but after exercise the respective muscles became hard and shortened, and developed areas of painful swelling. On resting the condition gradually improved and returned to normal. Passive extension of the affected muscles during this time met with considerable resistance and was painful. Electromyography revealed no activity at rest, normal action potentials during contraction and the painful areas of shortened muscle were electrically silent. McArdle compared the muscles in this case to the muscle in cases of iodioacetate and heavy metal poisoning and showed that the defect in his case was due to defective glycolysis. This was thought to be due to failure of the sulphydryl-splitting enzymes. McArdle gave his patient Dimercaprol with definite improvement, which was unfortunately shortlived. The defective glycolysis in McArdle's case has now been localized to a deficiency of phosphorylase, and the temporary improvement to Dimercaprol remains a mystery (McArdle, 1960). This and similar cases are obviously very different from the cases described in this paper which gave no evidence of defective glycolysis but are characterized by continuous muscle-fibre activity. The shortlived improvement following on Dimercaprol in Case 1 is, as with McArdle's case, difficult to explain.

Moersch and Woltman (1956) recorded 14 cases described as the 'stiff-man' syndrome. These cases were collected over a period of 30 years and included four women. The conditions appeared usually in the fifth decade with gradually increasing rigidity associated with intermittent painful spasms which could be precipitated by external stimuli or sudden voluntary or passive movement. The muscles first affected varied from those of the trunk, neck, and shoulders to those of the extremities, eventually spreading to involve all except the jaw muscles. The ultimate picture demonstrated marked involvement of the proximal musculature and to a lesser extent the distal. The muscles were described as rigid and board-like, fluctuating in severity. The tendon reflexes were brisk. An undetermined reducing substance was found in the urine of four cases, otherwise biochemical investigations were normal. Electromyographic studies in five cases gave a normal pattern. Muscle biopsy findings in two cases were normal. The conditions failed to respond to barbiturates, cortisone, antispasmodics, and relaxant drugs; 11 cases were followed for periods up to 15 years. There was a gradual deterioration in each. The severe proximal muscle involvement, the sparing of the jaw muscles, the brisk tendon jerks, the severe intermittent spasms with agonizing pain, the normal electromyographs and muscle biopsies, absence of fasciculation, increased B.M.R., and involuntary contraction of muscle fibres serve to distinguish the 'stiff-man' syndrome from the syndrome of continuous muscle-fibre activity.

There are some points of similarity between the

cases with continuous muscle-fibre activity and the myotonic disorders of muscle. Continuous muscle-fibre activity is slightly aggravated by cold, a feature shared by a large number of myotonia sufferers. After strong voluntary contraction of any muscle there is a sustained shortening of the muscle lasting long after the initial stimulus has stopped, as in myotonia, though the mechanism is entirely different. In the former the shortening is maintained by persistent contraction, whereas in the latter it is a delay in relaxation. With continuous muscle-fibre activity the first movement is usually the most difficult to overcome but eases on repetition, whereas, at other times the first few movements are relatively free, becoming more difficult with repetition up to a point after which the movement becomes easier. The former progression is common in myotonia, and the latter, though rare, is occasionally seen and has been referred to as paradoxical myotonia. If the first movement, however, represents a maximum contraction, it is doubtful if this paradoxical progression exists. Marshall (1952) described a curious case of paradoxical myotonia in which the failure to respond to quinine or deteriorate with potassium, together with the absence of myotonic response to percussion makes one wonder whether this is in fact myotonia and not a variant of continuous muscle-fibre activity. The rates of discharge of electric activity vary between 5 and 250/sec. which covers the myotonic range.

There are many points of distinction between these cases of continuous muscle-fibre activity and those with myotonia. Patients with myotonia are normal at rest, whereas those with continuous muscle-fibre activity show continuous muscular activity in both the waking and sleeping states. Electrical activity virtually ceases in myotonia with the onset of relaxation, with the exception of a low-voltage after-discharge and the occasional phenomenon of reflex afterspasm (Denny-Brown and Nevin, 1941). The cases under discussion show continuous high-voltage electrical activity at rest, recruiting with voluntary effort, but on relaxation the activity continues for some time well above the abnormal pattern which was present before the voluntary contraction. The activity at rest is not affected by local blocking of the motor nerves. In contrast to myotonia, the activity of continuous muscle-fibre activity is abolished by blocking conduction at the motor end-plates. The electrical activity at rest in continuous muscle-fibre activity does not have the appearance of normal motor unit potentials, but suggests bizarre spontaneous contraction of large numbers of muscle fibres. A notable feature in these cases is the lack of response to direct mechanical stimulation as opposed to that which occurs in the case of myotonia. These cases of continuous muscle-fibre activity have obvious fasciculation involving all muscles in varying degree, whereas fasciculation is rarely if ever seen in myotonia. In myotonia, the abnormal electrical response occurs only with the initial shortening of the muscle and not with sustained contraction, so that relaxation, though not necessarily complete, must be attempted before the myotonic discharges can be reproduced with further movements of that muscle. Though aggravated severely by contraction, patients with continuous muscle-fibre activity actively maintain a persistent discharge at all times with the exception of a curious period of dampening down of electrical activity approximately half a minute after a strong contraction and lasting for about 10 seconds. This dampening down is not a manifestation of fatigue and might suggest that some product of muscle nerve metabolism or motor end-plate activity is responsible for the apparent improvement.

Localization of the lesion is aided by noting that the persistent activity continues after interruption of the lower motor neurone by local nerve blockade. This would tend to take the lesion beyond the peripheral nerve, with the exception of the terminal network which seems to possess, in addition to the conductive function of the nerve, certain peculiarities of its own and may be the site of abnormal electrical discharges. The electromyographic studies would support the fact that the discharge is occurring from a site within the terminal branchings or the myoneural junction itself.

The possibility of a primary muscle cell membrane disorder is excluded by the response obtained with myoneural blocking agents, barbituric acid derivatives, quinine, and the absence of irritability to needle electrodes or to percussion.

Evidence of abnormal function at the myoneural junction is shown by the increased sensitivity to the competitive blocking action of d-tubocurare. This finding suggests either excessive destruction of or an inadequate production of acetylcholine. Both these conditions are made improbable by the presence of continuous muscle activity, the fasciculation of the muscles, the failure to respond to prostigmine or quinine, and the normal pseudocholinesterase level. An alternative explanation for this increased sensitivity to curare suggests that the motor end-plate itself may have become relatively resistant as a result of the continuous acetylcholine stimulation, a phenomenon which was demonstrated by Brown (1938) and more recently by Thesleff (1955). The response to calcium and magnesium may further indicate the presence of a somewhat resistant motor end-plate. When given parenterally these substances produced marked weakness in dosages which

did not affect normal controls. Magnesium suppresses the formation of acetylcholine in the nerve endings, while high calcium dosage increases the resistance of the motor end-plate (Brink, 1954). Carcinoma of the bronchus may be associated with extreme sensitivity to curare as shown by Eaton and Lambert (1957) so that unknown substances acting at the myoneural junction must also be kept in mind as a possible explanation for this finding.

Fasciculation may occur with lesions at the myoneural junction as is seen following the administration of depolarizing drugs. The electromyographic findings during this period resemble the discharge of continuous muscle-fibre activity, including the occasional motor unit potential formed by antidromic spread along the terminal branches as shown by Masland and Wigton (1940). With depolarization of the motor end-plate, however, there occurs a resistance to the action of blocking agents as opposed to the increased sensitivity in patients with continuous muscle-fibre activity.

Most of the evidence would favour an abnormal discharge from the terminal network of the motor neurone or myoneural junction with antidromic spread giving rise to fasciculation. The response to hydantionates in restoring these cases for practical purposes to normal would also favour an abnormal neuronal discharge rather than a metabolic defect at the myoneural junction.

Finally, in addition to these observations the modulating influence of the central nervous system must be considered. Lesions affecting central control may possibly result in the loss of specific inhibition affecting the production of mediating substances in the terminal network or myoneural junction, as was suggested for the lower motor neurone by Eccles (1957). Eccles was of the opinion that substances such as strychnine and tetanus toxin act by blocking an inhibitory transmitter substance in the lower motor neurone.

Considering the available information on these cases with continuous muscle-fibre activity, one concludes that a defect has been acquired at the level of the terminal network of the lower motor neurone, producing the bizarre and persistent neural activity which may be demonstrated electromyographically as a uncoordinated pattern of continuous muscle-fibre activity. This phenomenon is shown to be independent of transmission from the proximal part of the lower motor neurone and central nervous system though temporarily aggravated by voluntary movement.

The bizarre uncontrolled discharge from the terminal network has been restored to normal by the use of the anticonvulsant drug sodium hydantoinate which acts principally by increasing the sodium pumping action of nerve and muscle tissue as shown by Woodbury, Koch, and Vernadakis (1958).

Summary

Two cases demonstrating a syndrome of continuous muscle-fibre activity are presented and discussed, together with a therapeutic approach which has virtually restored normal mobility.

The syndrome is acquired, one case occurring in childhood and the other in middle age. The condition is separated from the group of myotonic disorders and some aspects of aetiology are discussed.

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ELECTROENCEPHALOGRAPHIC CHANGES IN CEREBELLAR DEGENERATIVE LESIONS

BY

L. A. LIVERSEDGE and V. EMERY

From the Departments of Neurology and Encephalography, University of Manchester, Manchester Royal Infirmary

Following the rapid extension of electroencephalography in the investigation of all forms of intracranial affection in clinical neurology, it soon became apparent that tumours in the posterior fossa greatly complicated the electroencephalogram. Numerous early publications, including the work of Grey Walter (1936, 1937, and 1938) and that of Bickford and Baldes (1947), gave conflicting information and seemed only to indicate that there was no pattern of electrical abnormality characteristic of a posterior fossa disturbance. However, Bagchi, Lam, Kooi, and Bassett (1952) reported their electroencephalographic experiences over a period of seven years gained from examining 37 patients, all of whom had proven posterior fossa tumours. Their findings indicated that 32 of these patients had abnormal records and that the abnormality consisted either of background slowing or of burst activity of one type or another, or else a combination of the two. Bagchi and his associates were not able to say what clinical or pathological factors were definitely responsible for these E.E.G. abnormalities. They thought that in any particular case neither the size nor the character of the tumour could be related either to the degree of slowing or to the prominence of the burst activity. Daly, Whelan, Bickford, and McCarthy (1953) found that the principal electrical abnormality seen in their series (comprising 66 patients with tumours of the posterior fossa, 12 who had tumours of the third ventricle, and a further nine who had obstructive hydrocephalus), consisted of rhythmic bilateral synchronous slow waves, though less often irregular arrhythmic waves might be seen. In this series they could find no correlation between the electroencephalographic abnormalities and the site of the lesion. Daly suggested, therefore, that hypertension in the third ventricle was of importance in the production of these abnormal rhythms. Dow (1956), reviewing this problem, concurred with this notion of third ventricular hypertension, but, as Bagchi *et al.* (1952) had pointed out, there are a number of ways in which the expansion of an infratentorial lesion may produce a change in the electroencephalogram. In the first instance the postero-inferior portions of the cerebrum may be subjected to direct contiguous pressure from the cerebellar tumour. Secondly, progressive obstruction to the outflow of cerebrospinal fluid may produce the third ventricular hypertension to which allusion has been made. Finally, however, we must not forget that involvement of the cerebello-cerebral pathways may influence remote cerebral electrical activity and so produce a disturbance of the normal electroencephalographic patterns. The anatomical and physiological relationships between cerebral and cerebellar activity have been clearly demonstrated by the work of Smyth (1941), Snider (1950), and Snider and Eldred (1952), and leads to the suggestion that there will be some electrical interplay between the various connexions. Apart from the information available in relation to posterior fossa tumours, there is little or no evidence of the way in which other pathological processes in the posterior fossa may influence the E.E.G., although Moruzzi and Magoun (1949) have indicated that the reticular formation may well have a large part to play in the production of normal cerebral electrical activity, and, therefore, of abnormal cerebral electrical patterns. Yet Russell Brain and Strauss (1955) include amongst disorders in which no electroencephalographic abnormality is noted, the degenerations of the cerebellum and of the spino-cerebellar pathways. For this reason it was thought that it would be profitable to collect what information might be available on the subject of E.E.G. recordings in relation to cerebellar and spino-cerebellar disturbances which are not primarily due to tumours. We have been able to collect evidence of this nature in 21 patients on whom electroencephalography was carried out.

Clinical Material

Greenfield (1954) pointed out that it is not always possible, indeed it is rarely possible, to establish with certainty in life the particular type of cerebellar

disorder to which a given case belongs. In his monograph, however, he divided the spino-cerebellar disorders into three main groups, namely, (1) predominantly spinal forms, (2) spino-cerebellar forms, and (3) predominantly cerebellar forms.

We have found it possible and convenient to group the 21 patients seen in this study under these three broad headings: two of the 21 belong to the spinal group, four to the spino-cerebellar, and the remaining 15 to the predominantly cerebellar types (Table I).

It was very interesting to note that in the spinal types the electroencephalographic recordings were within normal limits, the only notable feature being that random theta activity was present. In three of the four spino-cerebellar patients again the only abnormality noted was the tendency for theta outbursts to be present. The fourth of these (Case 6), who exhibited a pronounced cerebellar defect and also optic atrophy, in addition to the spinal manifestations, later developed epileptic attacks, both generalized and myoclonic in type. The E.E.G. in this case contained a good deal of high-voltage delta activity, situated in the posterior temporal and parieto-occipital areas on both sides. The interest of these findings hinges largely on the fact that the degenerative lesions of spinal distribution only do not appear to produce any form of electrical abnormality, and only cases with added cerebellar features develop abnormal electrical patterns. It is, therefore, all the more significant that one finds in group 3 (the predominantly cerebellar group) very definite E.E.G. disturbances. Table I summarizes the principal clinical findings in these cases, which include, in addition to the cerebellar degenerative disorders, one case of hyperpyrexial cerebellar degeneration, one case of left-sided cerebellar infarct, and three patients in whom myoclonic manifestations were present in addition to the obvious cerebellar defect. In three other cases the clinical evolution showed that, at a later stage, there was an extension of the disorder to extrapyramidal pathways other than the cerebellar connexions. The possible significance of this will be discussed later.

Analysis of the Cerebellar Group.—We discovered that in 13 of the 15 cases in this group, there was evidence of electroencephalographic abnormalities, which may be summarized as follows:—

(1) A tendency for slowing of the dominant rhythm in 12 of the 15, with forward spread of this rhythm in 11 of these; (2) an excess of theta activity in all 15 of the cases; (3) delta activity was noted in 12 cases, and in four of them it was at times focal. In six cases the delta activity was bilaterally synchronous, its situation being in two cases posterior, in two anterior, and in two central. In the three other cases of the group some delta activity was noted, but it was not very prominent. It is to be noted that the theta and delta activity could be inhibited by visual stimuli in four of the 15 cases. We were particularly interested to observe that in Case 9, in which there was an infarct in the left cerebellar lobe, these abnormal features were very prominent, for the dominant rhythm was between 4 and 7 c/s, and there was delta activity which was bilaterally synchronous. Both of these frequencies were inhibited by visual stimuli. In Case 11, where the cerebellar defect was the result of a hyperpyrexial episode, the dominant rhythm was 8 to 9 c/s, there was diffuse theta activity maximal in the frontal areas, and some scattered delta activity, which was inhibited to some extent by visual stimuli.

We have already alluded to the fact that in three cases clinical affection of the basal ganglia was detected. In these cases there were no great differences in the records from those in which the disorder was confined to the cerebellum, and it seems that here, as is also the case in typical Parkinsonism, there is no great change in electroencephalographic patterns as a result of the affection of the basal ganglia themselves.

Correlation between Clinical Features and Electroencephalographic and Post-mortem Findings

Post-mortem examination was carried out in Cases 7, 10, and 21. We feel, therefore, that more detailed analysis of these three cases is indicated.

Case 7.—G.B. was a man aged 50. In 1950 this patient, a keen and proficient darts player, first experienced difficulty in maintaining his high degree of accuracy at the game. Within two to three months he developed unsteadiness of the legs, and thereafter the coordination of the upper and lower limbs gradually deteriorated. In 1951, he experienced great difficulty with writing and began to have 'jumping' (myoclonic jerks) in both knees. The family history was not contributory. Examination on August 10, 1951, revealed that abnormalities, confined to the nervous system, comprised unsustained bilateral nystagmus, slight slurring dysarthria, generalized hypotonia, intermittent bilateral myoclonus of the hamstrings, dysdiadokokinesia, and impaired finger-nose and heel-shin tests.

Analysis of the cerebrospinal fluid, radiographs of the skull and chest, and a Wassermann reaction and blood count all proved normal. No electroencephalogram was performed at that time.

During the next four years the condition steadily deteriorated and additional signs of a striatal type of tremor, with associated cog-wheel rigidity, supervened. He was re-admitted to hospital on July 1, 1955, when routine investigation again proved quite normal with the

TABLE I

CLINICAL FINDINGS IN PRESENT SERIES GROUPED ACCORDING TO GREENFIELD (1954)

Case No.	Sex	Age	Duration of Illness in Years	Clinical Diagnosis	Principal Clinical Features	E.E.G. Findings
Spinal Group						
E.T. 1	F	45	18	Heredo-familial spastic paraplegia	Ataxia, deafness, bilateral pyramidal signs	Within normal limits
D.D. 2	M	10	3	Friedriech's ataxia	Ataxia areflexia, pyramidal signs	Random theta activity 3·5 to 7 c/s Within normal limits for age
Spino-cerebellar Group						
W.C. 3	M	61	9	Spino-cerebellar degeneration	Slurring speech, ataxia, nystagmus, pyramidal signs	Alpha rhythm 7 to 10 c/s, random theta activity, probably within normal limits
J.D. 4	F	25	4	Heredo-familial spastic paraplegia	Slurred speech, intention tremor, nystagmus, pes cavus, pyramidal signs	Within normal limits
H.A. 5	M	48	5	Spino-cerebellar degeneration	Tremor of voice, ataxia, diminished reflexes, pyramidal signs	Alpha rhythm widespread 7 to 11 c/s, diffuse theta 3·5 to 6·5 c/s anteriorly
A.T. 6	M	30	16	Heredo-familial spinocerebellar degeneration, epilepsy	Unsteadiness, nystagmus, dysarthria, optic atrophy, pyramidal signs, myoclonus	Diffuse theta 4 to 7 c/s activity high-voltage delta 1·5 to 3·5 c/s activity, widespread reduced by visual stimuli, and focal to right posterior region
Cerebellar Group						
G.B. 7	M	50	7	Olivo-ponto-cerebellar degeneration	Unsteadiness, nystagmus, tremulous voice, later striatal tremor, cogwheel rigidity	Widespread dominant rhythm 6 to 8 c/s, delta and theta activity focal in left superior frontal and right posterior temporal areas, inhibited by visual stimuli
G.W. 8	M	20	3	Cerebellar degeneration, major epilepsy	Ataxia, tremor, myoclonic jerks, epilepsy	Dominant rhythm 7 to 10 c/s, slow activity 2·5 to 6 c/s, more pronounced and focal in right parietal region than left. This slow activity is inhibited by visual stimuli.
H.J. 9	M	40	1 week	Rheumatic heart disease, mitral stenois, left cerebellar infarct	Unconscious, bilateral pyramidal signs	Dominant rhythm 4 to 7 c/s, bilaterally synchronous delta activity 1·5 to 3 c/s in all areas, but maximal in anterior leads
M.N.10	F	71	9 mth.	Cerebellar atrophy	Slurring speech, ataxia of limbs and trunk, areflexia, no pyramidal affection	Dominant rhythm widespread and irregular, 4 to 9 c/s, random delta 1·5 to 3·0 c/s throughout the record
W.S. 11	M	44	3 mth.	Hyperpyrexial cerebellar degeneration	Septicaemia, temp. 105° F., delirious for 4 weeks, ataxia, slurred speech	Dominant rhythm 8 to 9·5 c/s, intermittent theta 4 to 7 c/s, scattered delta 2 to 3·5 c/s, maximal in posterior regions, symmetrical and inhibited by visual stimuli
J.L. 12	F	18	4	Cerebellar degeneration	Ataxia, nystagmus, tremulous speech, diminished tendon reflexes	Dominant rhythm 8 to 10 c/s, irregular delta 30 c/s, symmetrical in occipital areas, intermittent symmetrical theta 4 to 7 c/s
F.P. 13	F	31	10	Cerebello-spinal degeneration	Ataxia, hypotonia, slurred speech, deafness, pyramidal signs, myoclonic jerks	Dominant rhythm widespread 7 to 10 c/s, theta 5 to 6 c/s all areas, occasional delta wave with focal spike in left midtemporal region
N.S. 14	F	57	10	Cerebello-spinal degeneration, 'Marie's ataxia'	Ataxia, optic atrophy, slurring speech, pyramidal signs, nystagmus	Dominant rhythm 7 to 8 c/s widespread, 4 to 6·5 c/s maximal in anterior leads, 2 to 3·5 c/s maximal in anterior leads. These rhythms were reduced by visual stimuli. Overbreathing accentuated this delta and theta activity and produced a phase reversal in the right posterior parietal area.
J.A. 15	F	28	10	Cerebello-spinal degeneration	Ataxia, nystagmus, slurring speech, hypotonia, absent tendon jerks	Dominant rhythm 7 to 10 c/s, frequent runs of slow waves 3 to 3·5 c/s focal to left midtemporal area, random theta 4 to 7 c/s
P.H. 16	M	60	7	Olivo-ponto-cerebellar degeneration	Ataxia, pale discs, tremor hands, pyramidal signs	Dominant rhythm 7 to 9 c/s disorganized in all areas by 4 to 6 c/s theta and 2 to 3·5 c/s delta. The slow waves are maximal in posterior leads.
W.B. 17	M	51	15	Cerebellar degeneration, severe head injury before the onset of symptoms	Ataxia, dysarthria, hypotonia, intention tremor	Within normal limits
T.So.18	M	56	5	Cerebellar degeneration with Parkinsonian features	Ataxia, dysarthria, intention tremor, Parkinsonian tremor, rigidity	Within normal limits
T.Si. 19	M	21	11	Cerebellar degeneration, myoclonic epilepsy, major epilepsy	Dysarthria, ataxia, myoclonic jerks (pneumoencephalography normal)	Dominant rhythm 4 to 7 c/s, frequent bilaterally synchronous delta activity 1·5 to 3 c/s
B.W. 20	F	42	6 mth.	Ovarian tumour ? cerebellar secondary	—	Within normal limits
J.K. 21	M	61	2½	Cerebellar degeneration, secondary to pulmonary neoplasm	Dysarthria, ataxia, diplopia, mental changes	Theta focus in vertex, dominant rhythm 8 to 14 c/s asymmetrical, 3 to 7 c/s slow outbursts right side

exception of the electroencephalogram. The dominant rhythm was slow (6 to 8 c/s) and widespread. Medium voltage slow waves at 3·5 c/s occurred in all areas, frequently out of phase in the left frontal and left posterior temporal regions. His clinical condition continued to decline and he died on July 31, 1955. At no time was there any clinical evidence of affection of the pyramidal pathways, and his mental status was preserved throughout.

Dr. P. O. Yates, who carried out the necropsy, reported that the brain arteries were slightly atherosclerotic, the cerebellum was smaller than normal, the pons and inferior olives appeared atrophic.

The cerebellar folia showed in many places marked atrophic changes with loss of Purkinje cells and reduction of the granular layer. This change was scattered and does not show any regularity of pattern. Bergman's cells were increased in number and there were more gliotic nuclei in the molecular layer of the involved folia. The white matter showed a diffuse loss of myelin appropriate to the loss of neurones, with gliotic sclerosis. There were no particular changes in the structure of the dentate nuclei. The pons was very small and showed a moderate degree of gliosis, diffusely spread towards the medulla. There were a few foci of demyelination. The olivary nuclei did not show any pronounced changes, apart from a slight demyelination of nerve fibres. There was a slight diffuse gliosis throughout the medulla. The nuclei of both striothalamic groups showed increased satellitosis with slight gliosis. There was no change in the ganglion cells. Sections taken from the cerebrum showed no significant histological abnormality.

In short, a patient in whom there was widespread progressive affection of the cerebellar area with no obvious histological affection of the cerebrum, showed in life these definite changes in the electroencephalogram.

Case 10.—M.N. a woman, aged 71, in July, 1953, began to exhibit unsteadiness of gait which rapidly deteriorated so that within six months she was bedridden. She soon became ataxic in the trunk and upper limbs, and developed a slurring dysarthria. Examination on February 26, 1954 (Dr. G. E. Smyth), showed that the patient was quite uncooperative; she was extremely ataxic with irregular tremors of the hands at rest. The limbs were hypotonic. All reflexes were absent. Plantar responses were flexor. Investigations at that time revealed that abnormalities were again confined to the electroencephalogram. The record was dominated by a medium voltage moderately sustained irregular activity at 4 to 9 c/s fairly symmetrical and synchronous, but abnormally widespread. It was frequently displaced by medium to high-voltage delta waves at 1·5 to 3·5 c/s appearing at random throughout the record and often underlying the dominant rhythms. Occasionally a low-voltage fast activity was noted. Her condition deteriorated rapidly and she died on April 10, 1954.

Dr. P. O. Yates carried out the necropsy and reported that a moderate degree of atheroma was seen in the coronary, carotid, and cerebral vessels. The cerebrum appeared normal. The cerebellar folia appeared shrunken throughout both hemispheres uniformly.

In various sections from the cerebrum there was no detectable abnormality. The cerebellum showed a thinning and loss of the granular layer. Purkinje cells appeared normal. Myelin was lost in the folia. The thalamus appeared normal, as did the spinal cord.

Once again, therefore, the widespread electroencephalographic changes appear to have been associated with degenerative changes in the cerebellum, producing quite marked clinical cerebellar dysfunction.

Case 21.—J.K., a man, aged 61, in 1946 developed a left-sided hemiparesis of sudden onset from which he made a full recovery within the space of three months. In February, 1954, he became constipated and began to lose weight. In May, 1954, he became unsteady and experienced difficulty in focusing. Shortly after this he became dysarthric and his gait rapidly more ataxic. His hands and arms also developed incoordination. Examination on July 27, 1954, showed sustained bilateral coarse nystagmus, dysarthria, ataxia of the arms, trunk, and legs, slight diminution of the left ankle jerk. Plantar responses were equivocal.

A barium meal and a barium enema were normal. A radiograph of the chest was normal but one of the pelvis showed Paget's disease. The serum alkaline phosphatase was 31·5 units/100 ml. Cerebrospinal fluid was normal on resting pressure, and a cell count gave 14 lymphocytes, 1 mononuclear cell/per c.mm., protein 60 mg./100 ml., globulin slight opalescence, Lange curve 1123210000. An electroencephalogram on July 2 showed that the dominant rhythm was a well-sustained medium to high-voltage alpha activity at 8 to 9 c/s. This activity was asymmetrical, spread well forward, and its higher voltage components were blocked by visual attention. The highest voltage slower alpha components, together with some medium to high voltage slow waves, at 3 to 7 c/s often appeared in short bursts and were out of phase in the central, parietal, and mid-temporal areas on the right side, one short burst at 3 c/s being of high voltage and focal in the centro-parietal leads. A repeat E.E.G. on September 17 showed a medium to high-voltage, well-sustained alpha rhythm at 8 to 11 c/s still asymmetrical, spreading well forward and blocked by visual attention. Medium voltage theta activity at 4 to 7 c/s was fairly prominent. Long runs of bilaterally synchronous medium voltage theta waves at 4 to 5 c/s appeared in the temporo-occipital leads, and were sometimes, but not always, more frequent on the right side. There were also infrequent bursts of a complex mixture of alpha, beta, theta, and delta waves out of phase in the right midtemporal area.

On clinical grounds a diagnosis of a subacute cerebellar degenerative process, probably secondary to an undisclosed neoplasm, was made. The patient was discharged and his subsequent course followed as an out-patient and later as an in-patient at the Withington Hospital, Manchester, where he was admitted under the care of Dr. Greenwood. The patient did not die until February 10, 1956.

We are indebted to Dr. T. A. White for the post-mortem report. 'The brain appeared superficially normal, and was fixed whole for further examination. Bronchopneumonia was noticed and, in addition, all the major bronchi were surrounded by a tumour which appeared to have originated near the region of the left upper main bronchus. The glands around the trachea bifurcation at the lung hilum were replaced by a solid rather nodular mass of white growth, which proved to be an oat-cell carcinoma. Sections from the cerebrum were normal, and from the cerebellum showed widespread loss of Purkinje cells with a granular ependymitis in the fourth ventricle. There was a little lymphocyte cuffing round some of the vessels. These findings are not inconsistent with Marie's degeneration.'

Discussion

As was indicated earlier, there has been some difficulty in explaining the abnormal wave patterns in posterior fossa tumours. Williams (1939) believed that oedema was responsible for the slow wave abnormalities and Scarff and Rahm (1941) showed that ventricular decompression resulted in rapid disappearance of the slow waves. Bagchi *et al.* (1952) stated that the background slowing and burst activity appeared most often in the cases with the most marked ventricular dilatation. Bickford and Baldes (1947) suggested that the bursts of slow waves were due to excessive diencephalitic discharges produced by an expanding third ventricle. The theory of direct occipital compression was emphasized by Ecker (1948).

The findings in our cases appear to indicate that slow waves and background slowing are likely to occur in cerebellar lesions quite independently of an increase in intracranial tension, and suggest that the cerebello-central connexions may be important in the production of electrical patterns. These findings are particularly interesting when viewed in relation to experimental evidence on the subject, for Walker (1938) showed that stimulation of the neocerebellar cortex of the cat produced high-voltage, fast discharges in the opposite motor and premotor regions whilst Henneman, Cooke, and Snider (1948), employing the technique of evoked potentials, were able to show quite definite and extensive cerebello-cerebral relationships. It is not unreasonable to deduce, therefore, that a progressive defect of cerebellar structure will have its effect on the basic electrical patterns of the brain. An important corollary of these findings is that the identification of a posterior fossa lesion as space-occupying or degenerative in character must depend upon evidence other than electroencephalography, since the abnormal patterns displayed may occur in either type of lesion.

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STUDIES IN SPINA BIFIDA CYSTICA

I GENERAL SURVEY AND REASSESSMENT OF THE PROBLEM

BY

PATRICIA ANNE DORAN and A. N. GUTHKELCH

From the Royal Manchester Children's Hospital, Pendlebury, near Manchester

Nicolai Tulp, the physician whose features are immortalized in Rembrandt's painting 'The School of Anatomy', first suggested the name 'spina bifida' (Tulpius, 1652), though the condition was known to Hippocrates, and the mediaeval Arab physicians are said (Denucé, 1906) to have specifically recognized the absence of the spinous processes in the affected area. Ruysch (1691) distinguished between the paralytic and non-paralytic forms of spina bifida cystica and came near to discovering its association with hydrocephalus when he remarked that the two, allowing for the difference in site, were almost the same disorder. The clear recognition of this association, however, had to wait for Morgagni (1769), and detailed description of the many varieties of spina bifida only began in the later nineteenth century (Marsh, Gould, Clutton, and Parker, 1885; von Recklinghausen, 1886).

The literature on the subject of spina bifida is already vast (for bibliography, see Ingraham, Swan, Hamlin, Lowrey, Matson, and Scott, 1943), and it is not without trepidation that we set out to increase it. We do so because not only is spina bifida cystica a common cause of disability in infancy and childhood, but also, as improved medical care allows more crippled children to survive into adult life, it may well become in the future an even greater medical and social problem than it is now (Nash, 1956). It was therefore decided to review a series of cases of spina bifida cystica seen during the years 1948-58. All but 10 of these have been traced and the minimum period of follow-up of the survivors is two and a half years.

Definition and Classification

We define spina bifida cystica as a congenital anomaly of development in which there is a defect of fusion of the posterior neural arch of one or more vertebrae accompanied by a protrusion of the membranes of the spinal theca, with or without the cord and nerve roots, beyond the expected limits of the spinal canal, or with an abnormal contiguity of these tissue with the skin or the external body surface itself. The second part of this definition is added so as to include those cases, sometimes termed myelocoele, in which, although the abnormal spinal cord is lying exposed in the mid-line of the back, there is no actual cystic protrusion. Rarely, of course, one may see examples of 'anterior spina bifida' in which the protrusion is through a cleft in one or more of the vertebral bodies, usually in the sacral region, but no such case occurred in the present series.

Classification of the various forms of spina bifida cystica is far from easy. From the point of view of morbid anatomy, it is perhaps most satisfactory to divide the cases according to the constituents of the sac, and the simplest division is into simple meningocoele, in which the swelling is composed simply of a herniation of dura and arachnoid filled with cerebrospinal fluid (C.S.F.), and myelomeningocoele, in which the sac also contains parts of the spinal cord and nerve roots. This is the classification which will be adopted in this paper, though it has the limitations of having no direct relationship to function in the neurological sense. Even when the cyst itself contains no neural elements, it may none the less be associated with the presence of abnormal neurological signs and of weakness of the limbs and sphincters. This is due to an underlying maldevelopment of the spinal cord itself, and in the course of removing these innocent swellings, we have on several occasions verified the existence of an underlying hydromyelia or diastematomyelia. Similarly, although the majority of cases of myelomeningocoele are associated with partial or complete paralysis, yet elements of the cord and nerve roots may enter into the composition of the swelling without any functional disability resulting. An interesting example of this is seen in the variety of spina bifida cystica which involves the cervical or thoracic regions of the cord, and which in the past has sometimes been termed a syringocoele. Here, there is a hydromyelia of the cord which usually extends for several

segments above and below the spina bifida deformity itself. At the level of the defective fusion of the neutral arches there protrudes a swelling which can be shown by careful dissection to be composed of two different sacs. The outer sac is lined by the dura and contains cerebrospinal fluid. Inside this there is a thin, red, more delicate swelling, which proves to be protruding from the mid-line of the posterior aspect of the cord, between the posterior columns themselves. It is made up of ependyma with a small number of ganglion cells in its walls. It is continuous with the dilated central canal of the cord but can safely be amputated without causing any damage to the latter. This lesion is not seen at lower levels, although the large and complicated myelomeningocoeles of the lumbar region often contains cystic spaces which are undoubtedly hydromyelic dilatations of the malformed cord.

Developmental Considerations

During the second week of foetal life the neural tube develops from surface ectoderm, the meninges from a mesodermal anlage, and the spinal column by a condensation of scleroderm around the notochord. 'The neural ectoderm detaches itself from the superficial ectoderm and gives rise through a thickening of its walls to the brain and spinal cord. The latter is formed by a process of uniform thickening in the walls of the caudal portion of the tube while the former results from the more rapid but uneven growth of the rostral portion. The transformation of groove into tube begins near the middle of the embryonic body, and from this point closure proceeds in both directions. The last points to close are situated at either end and are known as neuropores' (Ranson, 1959). This process is complete by the fourth week of intra-uterine life and the vertebral laminae are developed and fused by the eleventh week.

It is agreed that spina bifida is a result of a maldevelopment at this early stage of foetal life, and that it is a manifestation of some disturbance in the mechanism of closure of the neural tube, either of chromosomal origin or due to a noxious stimulus acting upon the organizer which determines its final form. The administration of massive doses of vitamin A to pregnant rats causes the appearance of a large number of offspring with congenital malformations, among these anencephaly and spina bifida (Cohlan, 1954), and craniorachischisis can also be produced in the same species by salicylate poisoning (Warkany and Takacs, 1959). In the rat, the critical time for the administration of the toxic substance, if spina bifida is to result, appears to be the tenth day after mating (Kalter and Warkany, 1961). Cameron (1957b) suggests that the primary disturbance may sometimes be related to the time of closure of the blastopore. Extreme retardation of this event under the influence of *x*-radiation can lead, in amphibia, to monsters with two spinal cords and rumps, while lesser degrees of retardation result in diastmatomyelia and spina bifida. Barry, Patten, and Stewart (1957) have shown that in the grosser degrees of spina bifida cystica associated with the Arnold-Chiari malformation there is an overgrowth of the tissue of the central nervous system, relative to its coverings, which they have identified early in intrauterine life in human foetuses. They consider that this overgrowth so broadens the embryonic spinal cord that the neural tube cannot completely close during the period in which the organizer which determines this closure is still operative.

Browne (1955) suggested that the spinal malformation was a result of an insufficient quantity of liquor amnii, the foetus being therefore subjected to abnormal mechanical pressures from the uterine wall. This would cause it to assume an attitude of hyperflexion with consequent malunion of the spinal laminae with or without herniation of the spinal contents but Browne's hypothesis cannot account for all cases of rachischisis since there is an 11 to 12% incidence of hydramnios in all pregnancies in which the infant is born with spina bifida and hydrocephalus (Stevenson, 1960). It is *a priori* difficult to believe that insufficiency of the liquor in early pregnancy is followed by an excess of it later on.

Table I shows the anatomical distribution of the spina bifida deformity in all our cases and shows no material differences from the findings of other workers. The much greater frequency with which spina bifida cystica affects the lower as against the upper parts of the spinal column is clearly shown. The ratio of simple meningocoeles to myelomeningocoeles is about 1:3·7 which represents a higher incidence of myelomeningocoeles than in the series reported by Ingraham and Matson (1954), but this is probably because these authors rarely admit to

TABLE I

SITUATION OF SPINA BIFIDA CYSTICA IN 307 CASES

Site	Simple Meningocoele	Myelo-meningocoele	Total
Cervical	6*	6	12
Thoracic	7	13	20
Thoracolumbar	3	29	32
Thoraco-lumbo-sacral	0	10	10
Lumbar	23*	77	100
Lumbosacral	13	83	96
Sacral	13	25	38
Totals	65	243	308

*One case had both a cervical and a lumbar meningocoele.

hospital cases of myelomeningocoele with paraplegia. An earlier paper from the same centre (Ingraham and Swan, 1943) gives a ratio similar to our own, though the figures are presented in a slightly different form.

It is well known that cases of spina bifida tend to run in families. For example, although the incidence of spina bifida is of the order of 2 to 3 cases per 1,000 live births (Record and McKeown, 1949; Stevenson and Warnock, 1959), the risk of the birth of another child with a congenital malformation of the central nervous system (anencephaly, hydrocephaly, or spina bifida) after the birth of a child with spina bifida is 7·29% (Record and McKeown, 1950). Edwards (1958), however, cautions against assuming that this in itself indicates a hereditary tendency, saying that the marked environmental variations in the frequency of spina bifida 'cast doubt on the necessity of advancing genetic causes to explain familial concentrations of cases'. Hindse-Nielsen (1938), examining a large series of cases of spina bifida collected from a number of Danish hospitals, found that there was a family history of the condition on the mother's side in 0·32% of cases but on the father's side in only 0·15%. His data can be criticized on the ground that they are probably incomplete, since he found a similar preponderance of all other associated congenital anomalies on the mother's side in his cases, and this is unlikely. We ourselves found a positive family history of spina bifida in 8·14% of our cases, but it was equally distributed between the paternal and maternal sides of the family. On the other hand, there was a larger number of female than of male spina bifida children who had a positive family history of the condition (Table II), though the difference is barely statistically significant. We also looked into the question of a family history of congenital abnormalities other than those of the central nervous system, and found it in 16 male against 12 female cases. This difference has no statistical significance.

TABLE II

FAMILY INCIDENCE OF SPINA BIFIDA CYSTICA

	Family		Totals
	Affected	Not Affected	
Males	7	138	145
Females	18	144	162
Totals	25	282	307
Percentage with positive family history	8·14	—	—

$\chi^2 = 4{\cdot}039$ n = 1 P ~ 4%

Maternal ill health during early pregnancy may cause maldevelopment of the foetus, the classical example being the effect of the virus of rubella in the first trimester of pregnancy (Gregg, 1941). In the particular case of spina bifida, however, the situation is unclear. Coffey and Jessop (1959) suggested that there is a high incidence of congenital defect of the neural axis in infants born to mothers who suffered from virus influenza during the first trimester of pregnancy but this has not been confirmed (Doll, Bradford Hill, and Sakula, 1960). There was, in this series, no evidence of any influence of maternal ill health during early pregnancy.

The sex incidence of spina bifida cystica shows some interesting features. It is generally agreed, and our own figures show (Table III), that females are more frequently affected by spina bifida cystica than are males. But at the time of conception the actual risk to the embryo of the development of spina bifida is higher for females than these figures suggest, for Record and McKeown (1949) also found that the ratio of males to females in spina bifida stillbirths was 120:182.

TABLE III

SEX INCIDENCE OF SPINA BIFIDA CYSTICA

	Males	Females	Totals
Simple meningocoele	32	32	64
Myelomeningocoele	113	130	243
Totals	145 (47%)	162 (53%)	307

There is some evidence that not only is spina bifida a commoner condition in females than in males but also that it tends to be a more serious one. Record and McKeown's (1949) figures for the sex ratio of spina bifida stillbirths, to which reference has already been made, show that the excess of female over male spina bifida pregnancies is larger for stillbirths than for live births, so that a larger proportion of female than of male spina bifida foetuses fails to be carried to term. This may indicate that in the female the degree of spina bifida, together with its associated deformities, is more frequently too severe to be compatible with survival than in the male. Tables II and IV show that a similar tendency is to be found, though to a less marked degree, in those babies which are born alive. In the present series, the excess of females is almost entirely in the group with the more serious degree of spina bifida, that is to say, myelomeningocoele. Morever, only 50% of all the females with myelomeningocoele were thought to be fit for surgical treatment as against 63% of all the males, and the proportion of survivors—40% and 46% respectively of the total cases occurring in females and males—shows a similar tendency. In making our selection for operative treatment, our

TABLE IV
COMPARISON OF SUITABILITY FOR OPERATION AND CHANCE OF SURVIVAL IN MALE AND FEMALE CASES OF MYELOMENINGOCOELE

Males				Females		
Alive	Dead or Untraced	Total		Alive	Dead or Untraced	Total
49	22	71 (63%)	Suitable for operation	46	19	65 (50%)
3	39	42	Unsuitable	5	60	65
52 (46%)	61	113	Totals	51 (39%)	79	130

criteria may perhaps have changed a little from time to time during the 10 years of the study, but there was never any conscious bias in favour of either sex. More will be said in a later section of this paper about the indications for the surgical repair of spina bifida, and the time at which the operation should be carried out. For the present, it is sufficient to note that the main contraindications were a complete paraplegia associated either with gross infection of the swelling or with a severe degree of hydrocephalus. In a children's hospital, there is, of course, no question of beds being more readily available for one sex than for the other, so that although a small number of patients died while waiting admission to hospital, it is unlikely that the mortality due to this cause was heavier in females than in males.

Clinical Findings

It has already been mentioned that even in cases of simple meningocoele there may be some degree of malformation of the underlying cord and spinal nerves, not necessarily limited to the area of the spina bifida itself, this association, together with the deformities to which it gives rise, being sometimes known as status dysrhaphicus. Accordingly, it is impossible to associate a single neurological syndrome with any particular sort of spina bifida occurring at a given level in the spine, except perhaps that complete failure of the neural tube to close (myeloschisis) is always associated with a complete, or at least a serious degree of, failure of conduction of nervous impulses through the affected area. In general, it may be said that in any large series of cases of spina bifida cystica, all varieties of neurological disturbance of spinal type may be seen, ranging from absence of a single tendon reflex, usually the ankle jerk because the lesion is so common at lumbo-sacral level, to a complete sensory and motor loss with absence of all reflex activity.

Associated congenital abnormalities both of the central nervous system and of other parts of the body occur in a large proportion of cases of spina bifida cystica. Two of the more important of these, hydrocephalus and diastematomyelia, form the subject of later sections of this communication. Craniolacunia was frequently seen in the cases of hydrocephalus; there also occurred one case of craniosynostosis, two cases of Klippel-Feil syndrome, and many examples of wedge vertebrae, hemivertebrae, and congenital absence of one or more ribs. Outside the central nervous system and its coverings there were instances of imperforate anus, webbing of the digits, cleft palate and hare lip, laryngocoele, congenital heart disease, and double ureter.

In those cases of spina bifida cystica which were associated with partial or complete paraplegia, deformities of the lower limbs were frequently found, of which the commonest were dislocation of the hip, flexion contractures of the hip, genu recurvatum, and paralytic talipes, the last most commonly of the calcaneovalgus variety.

Treatment

Tulpius (1652) appears to have been the first to attempt the surgical treatment of spina bifida cystica. He ligatured the base of the sac but the infant died. During the next two centuries there were sporadic reports of the treatment of the condition, usually with fatal termination, but there was no systematic attack on the problem until in 1882 a committee was set up by the Clinical Society of London to investigate spina bifida and its treatment, presenting its report three years later (Marsh *et al.*, 1885). One hundred and twenty-five cases were studied of which 66% were of myelomeningocoele; 54% of all cases were situated in the lumbrosacral region. Paralyses, talipes, and hydrocephalus were observed in association with a spina bifida in a significant number of cases, and a positive family history was obtained in four. The committee made a critical survey of methods of treatment then practised, including aspiration, excision, ligation, and the injection of sclerosing solutions. Treatment by aspiration of the swelling was thought to be inadvisable owing to the risk of introducing infection: of 46 patients thus treated, 30 succumbed. The results after ligation of the base of the sac of the spina bifida cystica were better, six dying but 10 patients benefiting. Excision was performed in 23 patients, seven of whom died. The committee, however, advised against both ligation and excision on the

grounds that these methods caused further deficit due to removal of neural tissue, and the treatment most favoured was the injection of a sclerosing agent into the sac, preferably 'Dr. Morton's iodo-glycerine solution' (Morton, 1877), and in a series of 50 patients so treated, 41 were said to have been 'cured'. The relative success of this procedure was thought to be due to its resemblance to a 'spontaneous cure' by epithelialization and cicatricization of the swelling.

After the turn of the century and with the development of aseptic technique, excision of the sac became the treatment of choice though LaFerte (1910) advocated preservation of the herniated skin and neural tissue and its invagination into the spinal defect. Keiller (1922) considered that LaFerte's method caused intraspinal adhesions and that turning in the surface ectoderm predisposed to the formation of inclusion dermoids. When the cord below the lesion was not functioning Keiller advocated excision of the dysplastic neural tissues en bloc.

A further modification in the method of excision was described by Penfield and Cone (1932), who thought that the sac of a spina bifida cystica actively absorbed cerebrospinal fluid and that its removal precipitated a state of hydrocephalus. They advised repair in such a way as to conserve the tissues of the sac by stripping them from the overlying skin and plicating them into a bundle within the spinal canal. The sac was then covered by a fascial slide or graft. Later, Penfield and Coburn (1938) recommended the release of the cord from the overlying tissues in an attempt to prevent cicatricial contraction and fixation, believing that it was the resulting traction on the cord which gave rise to the Arnold-Chiari malformation.

Surgical Technique.—Our technique is similar in most respects to that of Ingraham and Matson (1954).

The patient lies in the prone position, under a general anaesthetic administered by endotracheal tube. If the sac is so large that there is likely to be a large loss of blood or cerebrospinal fluid an intravenous infusion is set up before operation. Two curved incisions are made, one along either side of the long axis of the swelling so as to isolate it but to preserve as much normal skin as possible.

The incision is carried down to the paraspinal musculature, and the dural layer of the neck of the sac defined and freed. It is important to leave sufficient dura at its margins for watertight closure later. Such tissue as can be recognized as of neural origin is preserved as far as possible, dissected away from the overlying skin and from the edges of the dura and returned to the underlying spinal canal. The dura is now sutured over it so as to form a new theca.

If the amount of available dura is insufficient, a graft of lumbar fascia is used to complete the closure. No attempt is made, and indeed it is generally agreed that none is necessary, to close the spinal canal with bone, but flaps of lumbar muscle and fascia are usually turned in to strengthen the repair. Where it has been necessary to excise large amounts of unhealthy skin along with the swelling, such manoeuvres as undercutting the skin edges and the formation of rotation flaps are freely employed.

After operations on sacral bifida, particularly in small babies, faecal contamination of the wound has been a problem, but the use of waterproof plastic adhesive tape to seal the lower part of the dressing is of considerable assistance in preventing this complication.

The post-operative convalescence has usually been smooth. We feel that wound infection can best be avoided by adherence to two principles: (1) Postponing operation (unless rupture of the sac demands intervention as a matter of urgency) until it is soundly epithelialized, and (2) taking care to avoid tension on all suture lines. If a cerebrospinal fluid fistula develops to the point at which any large volume of fluid is lost it has been found best to reoperate forthwith, and close the gap in the dura, so as to avoid both ascending infection and possible serious depletion of water and electrolytes.

Time of Operation.—Very early treatment, that is to say operation on the spine within the first 48 hours after birth, has not in our experience constituted an advantage because there may be an increase in neurological deficit after operation, whereas in no case in which operation was postponed until after the neonatal period has there been any increase in neurological deficit during the time of waiting. The occurrence or imminence of rupture of the sac with massive escape of cerebrospinal fluid is an indication for immediate operation at any time: leakage of droplets of cerebrospinal fluid from the central area granulosa is less immediately fatal. We have encountered a 16-year-old girl whose lumbar myelocoele has leaked in this way throughout her life. In such a case the cerebrospinal fluid is escaping from the open end of a hydromyelic central canal, but ascending infection, and particularly generalized meningitis, does not necessarily occur.

Where the time of operation can be chosen, our usual practice has been to operate between the ages of 3 and 12 months. An aseptic procedure is facilitated by the prior epithelialization of the sac, the operation is better tolerated, and there is less

difficulty in mobilizing sufficient skin for adequate closure of the wound when the defect is large.

Whether or not to operate at all upon babies who suffer from the grosser forms of spina bifida cystica with complete paraplegia is a most difficult problem. In the past, the association of paraplegia with rapidly advancing hydrocephalus has usually been regarded as an absolute contraindication to treatment. One could expect almost all such infants to die of hydrocephalus, renal failure, or bed sores within a few years, even if infection of the sac itself with suppurative meningitis did not ensue. Nowadays circumstances are different. Although the surgical control of hydrocephalus cannot yet be guaranteed (Guthkelch, 1958), there has been a considerable advance in this field recently, while improvements in the care of paraplegics now make it not uncommon for patients with severe congenital spinal palsy to survive into adult life (Guttmann, 1957). Nash (unpublished communication) has suggested that the 'limit of salvageability'—to use his own phrase—in congenital spinal palsy is a complete cord lesion at the level of the tenth thoracic segment. This has been our own experience also, and in the absence of an extreme degree of hydrocephalus when the baby is first seen, or of associated congenital anomalies of other systems of the body which are incompatible with survival, we are now prepared to treat all cases of spina bifida cystica in which the level of complete paralysis is not above Nash's limit, together with such complications as may subsequently arise. Where, however, viability is in doubt, we tend to postpone operation on the spine until the baby is about 18 months old. At that age, a repair becomes desirable in order to facilitate nursing care, whatever the ultimate outlook.

Management of Congenital Spinal Palsy.—It is not proposed to describe our management of these cases in any detail. The usual conservative measures, including physiotherapy and splinting, are used in order to prevent contractures and other deformities of the lower limbs. Paralytic dislocation of the hip joint is always treated conservatively, since attempts at reduction and stabilization have been uniformly unsuccessful. There is, however, in cases of below-knee paralysis, a place for the operative correction of deformity and for the improvement of function by tendon transplantation, arthrodeses, and similar measures. Nineteen of our patients were submitted to one or more operations of this type. Others are able to walk with the use of leg-irons or callipers.

Lack of voluntary control over the bladder presents a problem in a number of patients with spina bifida cystica who survive beyond early infancy. In the first instance, manual expression of the bladder is carried out in hospital and the mother is instructed in the procedure so that she can continue it at home. As the children grow older, it is often possible to educate them to empty their bladders at fairly frequent and regular intervals, so as to avoid incontinence. Such patients are, of course, prone to infections of the urinary tract, though usually these have responded well to short courses of the appropriate antibiotics. Rather contrary to expectation, no male case in this series has required resection of the bladder neck to combat a persistently high residual urine. For incontinence in the male, the use of the Chailey urinal bag has proved very satisfactory.

In six female cases it has been necessary to form an ileal loop bladder with an abdominal stoma. In three cases the indication was a persistent dribbling of urine with intractable excoriation of the skin of the perineum and thighs. In three cases, in addition to incontinence, serial pyelograms carried out over a period of years showed an increasing hydronephrosis. All of these patients made a satisfactory recovery from the operation and are able to keep dry without difficulty. In two of the three cases with hydronephrosis, there has been an improvement in the appearance of the pyelogram.

In young babies, paralysis of the musculature of the pelvic floor rarely causes any interference with bowel habit, though occasionally in this series prolapse of the rectum occurred and required treatment. In the older children, however, we have fairly frequently observed episodes of 'overflow' incontinence due to chronic incomplete emptying of the lower colon and rectum. This has usually been brought under control by advice on the use of laxatives and the importance of regular defaecation. In some of the more chronic cases, however, it has been necessary to admit the child to hospital so as to evacuate the rectum before beginning habit training.

Hydrocephalus in Spina Bifida Cystica

Except for actual rupture of the sac, the most unfavourable prognostic feature in a case of spina bifida cystica is the development of progressive hydrocephalus. It is, therefore, of importance to inquire whether the performance of the operation of the spine has any influence on the subsequent development of this complication. As the risk is very small in cases of simple meningocoele, only six of our cases showing signs of hydrocephalus at any time, and all of these becoming spontaneously arrested within two months without any subsequent disability, the analysis has been confined to cases of myelomeningocoele.

Of the total of 242 such cases, operation was

performed in 135. Seventy-seven of these showed evidence of hydrocephalus at some time during their lives, as compared with 81 out of 107 cases in which no operation was advised. This comparison, however, means little in itself, since the decision to accept or reject for surgery was made partly on the basis of the presence or absence of active hydrocephalus when the patients were first seen. A more useful estimate of the importance of the part played by operation on the spine in causing hydrocephalus can be obtained in the following way:—

Of the total of 243 cases of myelomeningocoele occurring in infants and children of all ages, 112 or 46%, were already showing signs of hydrocephalus when first seen. The risk of hydrocephalus occurring without operation cannot be less than this figure, and must in fact be more, since the majority of patients were less than 3 months old at their first attendance and the risk of the development of hydrocephalus is known to continue until at least the age of a year. On the other hand, of 99 operated patients of all ages who showed no sign of hydrocephalus at the time of operation, this complication developed subsequently in only 41, and in 12 of these the onset of the hydrocephalus did not occur for more than a month after the operation and can therefore hardly be attributed thereto. Compared with this 29% incidence in the early post-operative phase, it can be seen (Table X) that out of a total of 77 patients with myelomeningocoele in whom repair of the spinal defect was advised but who developed hydrocephalus, 36 (47%) became hydrocephalic before the operation was in fact performed. These figures hardly suggest that the removal of a myelomeningocoele necessarily imposes a large additional risk of death from hydrocephalus.

At the same time, it would be wrong to suggest that operation on a myelomeningocoele can never be complicated by the development of acute hydrocephalic signs and symptoms. A small number of the early patients in this series undoubtedly died from this cause. The explanation lies in the fact that cases of myelomeningocoele are almost invariably associated with the peculiar deformity of the brain to which some reference must how be made.

Encephalo-cranial Disproportion.—Deeply as the name 'Arnold-Chiari malformation' is entrenched in the literature, we feel that the time has now come to replace it by a more descriptive term, and the phrase 'encephalo-cranial disproportion' seems to us, for reasons which will appear below, to yield more insight into the pathogenesis of the deformity. In any event, Arnold's (1894) description, in a single case, of the deformity which has so far borne his name is brief and unsatisfactory and actual priority of description belongs neither to Arnold (1894) nor to Chiari (1891) but to Cleland (1883) who, in describing a case of thoraco-lumbo-sacral myelomeningocoele with hydrocephalus, mentioned and illustrated the characteristic elongation of the cerebellar vermis and fourth ventricle. Chiari's (1896) later work was of course of fundamental importance, but his name is already associated with a completely different paediatric syndrome. The anatomical features of encephalo-cranial disproportion have been fully described elsewhere (*e.g.*, Norman, 1958) and only a brief summary follows.

It cannot be too strongly stressed that the congenital deformity which we are considering is one which involves the whole brain. Above the tentorium one finds that besides the actual dilatation of the ventricles, there is also an increase in the amount of tissue which comprises the cerebral hemispheres. The surface of each hemisphere shows excessive plication or microgyria. The tentorium cerebelli lies at a lower level than normal within the skull. It is unusually flat, and its incisura is large. The occipital lobes of the hemispheres often herniate through the incisura (Daniel and Strich, 1958).

Because of the caudal displacement of the tentorium, the proportion of the cranial cavity which is occupied by the posterior fossa is smaller than normal and the pons and medulla oblongata are flattened and there is hypoplasia of the cerebellum. In about a third of the cases there is a stenosis of the aqueduct of Sylvius, and the fourth ventricle is longer and thinner than normal in all.

The lower part of the medulla is herniated through the foramen magnum into the cervical spinal canal, the dorsal more than the ventral part. Over the dorsal medulla there is a prolongation of cerebellar tissue which proves to be continuous with the vermis. At its lower end this tongue of cerebellar tissue is bound down to the medulla by vascular fibrous adhesions. The lower end of the prolonged cerebellum, and consequently of the fourth ventricle, may be as low as the seventh cervical vertebra. The abnormally low position of the medulla results in an elongation of the lower cranial nerves and the cervical spinal cord is also displaced caudally, so that the cervical roots run upwards and laterally to their appropriate foramina. There is often a hydromyelia of the spinal cord, its dilated central canal communicating with the ventricular system by a pore at the lower end of the elongated fourth ventricle.

Chiari himself (1891) believed that the whole deformity of the hind brain was to be explained as the result of increased pressure within the lateral ventricles due to hydrocephalus—a sort of intrauterine pressure cone. This hypothesis, however,

fails to explain the increase in the volume of the cerebral hemispheres, the downward displacement of the tentorium even in cases where there is no evidence of obstruction of the aqueduct at tentorial level, or the relatively more severe elongation of the dorsal as against the ventral medulla. Penfield and Coburn (1938) and Lichtenstein (1942) considered that the deformity arose because abnormal fixation of the spinal cord to the fundus of the sac in a case of spina bifida cystica with myelomeningocoele caused traction on the hind brain, and literally pulled it out of the posterior fossa and into the cervical spinal canal. Lichtenstein also stated that when, at post-mortem examination, the spinal cord in a case of myelomeningocoele was released from its point of attachment to the skin, it would actually move upwards within the spinal canal, but Russell (1949) showed that this was only true if the dissection was performed with the infant's neck flexed, and that a similar movement could be demonstrated on flexing the neck of the normal individual. Moreover, if the traction theory were correct, there should be a progressive increase in the amount of downward displacement of each segment of the spinal cord from the hind brain to the level of the myelomeningocoele. Such, however, is not the case. The cervical segments are displaced caudally, but the upper thoracic segments are in their normal position. There is some slight degree of downward displacement of the cord immediately above the myelomeningocoele, doubtless due to traction, but this is dissipated within four to six segments (Barry *et al.*, 1957).

Browne (1955) regards encephalo-cranial disproportion as due to the mechanical effect of pressure of the uterine wall on the developing foetal head when the amount of liquor amnii is insufficient. This hypothesis, however, fails to explain the presence of heterotopic nodules of grey matter in the walls of the lateral ventricles and in the cerebellar white matter in these cases, and, as has been pointed out earlier in this paper, the common occurrence of hydramnios in pregnancies which give rise to infants with spina bifida and hydrocephalus is not easy to associate with a condition of oligamnios at any early stage of development. Thirdly, if encephalo-cranial disproportion is due to the developing brain being squeezed out of the skull and into the cervical spinal canal by pressure, it is difficult to see why, according to evidence cited below, the brain in these cases should actually be larger than normal. Finally, as List (1941) pointed out, the sites of maximum abnormality in cases of myelomeningocoele with encephalo-cranial disproportion tend to be at the points of closure of the anterior and posterior neuropores, and this fact in itself suggests an embryological origin.

The most satisfactory explanation of the pathogenesis of encephalo-cranial disproportion is that of Barry *et al.* (1957). These authors studied the brains of two foetuses of estimated ages from conception of 10 and 17 weeks respectively. In both there was evidence that the hind brain was more massive than that of a normal foetus of comparable age. In the older foetus, the cerebral hemispheres were disproportionately large also, and Barry and his colleagues (*loc. cit.*) point out that it is logical to assume that this overgrowth of cerebral tissue accounts for the caudal displacement of the tentorium cerebelli. The microgyria which is constantly found in cases of encephalocranial disproportion might well be the final result of the overgrowth of the cerebrum already referred to.

The practical importance of encephalo-cranial disproportion in the management of cases of spina bifida cystica with myelomeningocoele arises in two ways. First, the condition is associated with crowding of the medulla oblongata and cerebellar tissue into the foramen magnum, as well as with a stenosis of the aqueduct in some cases. Thus, there is a danger of obstructive hydrocephalus, and a sudden release of cerebrospinal fluid from the spinal theca during operation may lead to an acute impaction of the medulla and cerebellum within the foramen. Secondly, surgical interference may precipitate a meningeal reaction, due to the presence of blood and occasionally of bacteria within the cerebrospinal fluid pathways. This reaction causes further embarrassment to an already abnormal cerebrospinal fluid circulation and may lead to active hydrocephalus.

A detailed discussion of the surgical treatment of hydrocephalus in association with spina cystica is outside the scope of this paper. In some cases spontaneous arrest occurs, while in others continuous drainage of the excess of cerebrospinal fluid either externally for a few days, or, on a long-term basis into a body cavity or into the blood stream, can be of value. There is, however, one point which should be made. Reduction of ventricular pressure in cases of encephalo-cranial disproportion may fail to relieve the impaction of the hind brain within the foramen magnum and cervical spinal canal. In four of our cases, the intracranial pressure was satisfactorily controlled by surgical means for a period of weeks or months, nevertheless the infants eventually died in a state of chronic medullary failure. Necropsy confirmed that the ventricles were draining freely, but showed that there was severe crowding of the foramen magnum, the prolapsed cerebellar tissue being actually gangrenous in one case. On the other hand, there was one example of acute medullary failure with quadriplegia occurring within 48 hours of the

removal of a large myelomeningocoele in a 6-year-old girl. An immediate suboccipital decompression and laminectomy of the upper cervical vertebrae was performed, releasing the impacted hind brain. She made an uninterrupted recovery and has shown no evidence of hydrocephalus in the 12 years which have elapsed since her operation. None the less, routine suboccipital decompression, even combined with cervical laminectomy, has failed, both in our hands and in those of others (Ingraham and Matson, 1954), to control hydrocephalus permanently in infants suffering from encephalo-cranial disproportion, and both ventricular drainage and decompression may be necessary. There is a need for more work on this subject.

Diastematomyelia

In the survey made for the Clinical Society of London (Marsh *et al.*, 1885), it was found that of 125 cases of spina bifida, there were five in which a distinct osseous or osseocartilaginous outgrowth arose from the posterior aspect of the body of a vertebra under the bifid spines, and in three of them this outgrowth seemed to split the spinal cord into two. This was undoubtedly a description of the condition which is now known as diastematomyelia. Denucé (1906) described the pathological anatomy of a number of necropsy cases.

Herren and Edwards (1940) studied a series of 42 cases of spina bifida in which there was what they termed a reduplication of the spinal cord, a quarter of these being associated with a spur or band which traversed the spinal canal in an antero-posterior direction. They observed that the cord was split into two usually unequal parts, each of which contained a central canal with well-developed lateral columns and nerve roots but undeveloped medial columns. Believing that this splitting of the cord represented an abortive form of twinning, they termed the resultant deformity 'diplomyelia', and the use of this term has led to confusion in the literature, some writers apparently believing that diastematomyelia (splitting of the cord) and diplomyelia (reduplication or twinning of the cord) were separate entities. This point however, has been settled by Benstead (1953): it is possible to find examples of all degrees of twinning from simple longitudinal division of a short segment of the cord through cases in which the two segments of cord are each enclosed in a separate dural sheath and separated by a bony spur to those in which the reduplication is complete and the individual is a monster with twin rumps and twin spinal cords.

Diastematomyelia occurs more commonly in the grosser degrees of spina bifida cystica than is generally realized. Cameron (1957a) found a splitting of the cord in association with spina bifida cystica in about half of a series of 26 cases examined, and commented that this is about the same proportion as one finds if spina bifida is produced experimentally in the embryos of amphibia by retarding the time of closure of the blastopore (Cameron, 1957b). In the present series, diastematomyelia was only encountered eight times in the total of 197 cases operated upon, but it may well have been missed in others because of incomplete exploration of the spinal canal, and of course many of the cases with a very gross degree of spinal deformity were rejected for surgery and there is therefore no information about the details of their pathological anatomy.

In three of the cases, diastematomyelia was a chance finding during the routine closure of a myelomeningocoele. A central bony spur was found in two. All these three cases showed some degree of neurological deficit before operation, though there was no evidence of progression. After operation the neurological state remained unchanged.

Of the five cases in which the spina bifida cystica lesion was a simple meningocoele, diastematomyelia was found by chance in two, there being no pre- or post-operative abnormal neurological signs. The third was a female infant aged 6 months. She presented with a small lumbar meningocoele surrounded by a large patch of hair. The right foot was smaller than the left, and the right knee and ankle jerks were absent. *X*-ray examination showed the presence of a bony spur arising from the third lumbar vertebra and an exploratory laminectomy was duly carried out. The cord was found, as expected, to be bifid, with twin dural sacs, and the spur itself was tightly apposed to the lower end of the bifid section. It was removed without incident and a normal surgical recovery followed. The child now has little disability, except that one foot remains smaller than the other. Sphincter control is not impaired. The fourth case was a boy who was first referred at the age of 5 years with a very small lumbar meningocoele surrounded by a hairy patch. He had no neurological disability, but examination showed absence of the right knee jerk and an equivocal plantar response on the same side. A typical bony spur was seen at first lumbar level on *x*-ray examination. No immediate treatment was undertaken, but a year later he was beginning to complain of aching pain in the right leg when he tried to play games. Operation was now performed with similar findings to those in the previous case. Now, at the age of 15, the right knee jerk is still absent but he has never since been troubled by pain in the leg and plays games normally.

The fifth case, also a boy, was first seen at the age of 2 months, when he presented with a small

meningocoele at the thoraco-lumbar junction together with weakness and wasting of the left leg and a left-sided lumbar hernia. Initially, a very limited operation was performed, the neck of the sac being ligatured at the level of the inter-spinous ligament, and the spinal canal itself not explored. He was next seen 18 months later when his mother complained that there was increasing scoliosis, that he was not learning to walk, and that the wasting of the left leg was increasing. He was found to have a paralytic calcaneovalgus deformity of the left foot with an absent ankle jerk and equivocal plantar response on that side. His *x*-ray films were reviewed, and it was realized that there was a central bony spur at first lumbar level. The spine was therefore re-explored and the expected diastematomyelia discovered. The right half of the cord was normal, but the left half was rather thin. The bony spur was removed and a normal surgical recovery followed. This little boy is now walking satisfactorily, and the left plantar response is flexor.

This final case teaches the importance of a proper exploration of the spinal canal in every case of spina bifida which is submitted to operation, for there is no other way of excluding the presence of other lesions which may be amenable to surgical intervention. The presence of diastematomyelia with spur formation cannot be completely excluded by plain *x*-ray examination because the appearances are often slight and the spur itself may be fibrous or cartilaginous, and therefore not radio-opaque. Where the suspicion of diastematomyelia is entertained, the diagnosis can, of course, almost always be made by myelography. But sometimes this fails too. We have had one case (not associated with spina bifida cystica, and therefore not reported in detail in the present communication) in which the spinal canal was divided into two very unequal parts. The bony spur was not well defined, and at myelography none of the opaque medium could be persuaded to enter the smaller canal. Exploration was only decided upon after some hesitation and because the neurological lesion appeared to be progressive. The true state of affairs was then revealed.

Results

To discuss the prognosis in spina bifida cystica as if it were a homogeneous entity would be meaningless. It is universally recognized that the outlook in simple meningocoele is better than that in myelomeningocoele, but there is strong evidence in our figures that the reason for the difference lies in the greater risk of hydrocephalus associated with the latter condition rather than in the details of the spinal defect itself.

The ultimate outcome of treatment in the group of 64 children suffering from simple meningocoele needs little comment. Table V shows that the mortality is very low, the patient who died of meningitis being moribund when first seen. Two cases, recorded as untraced in Table V, were examples of simple lumbar meningocoele but the parents apparently moved away from Manchester during the time when their children were awaiting admission to hospital. It is very unlikely that these two infants are other than alive and well, and they have doubtless been operated upon in other units. None of the 61 traced survivors is seriously disabled. Three of the nine patients who show some degree of weakness of the legs were found at operation to have an underlying diastematomyelia, and this is plainly a lesion, the possibility of which should not be forgotten in any case of simple meningocoele with neurological signs. We have recorded that four patients suffer from some impairment of sphincter control, but two of them are under 3 years old, and as they have no abnormal neurological signs, they are likely to gain control of their habits in the near future. The other two are occasionally wet if they forget to empty their bladders at regular intervals, but neither is prevented from attending a normal school. A total of six patients developed some degree of increased intracranial pressure for periods of up to two months after operation, but all have settled down satisfactorily, and show no sign either of intellectual defect or of epilepsy.

TABLE V

FATE OF CHILDREN WITH SIMPLE MENINGOCOELE

	Operation	No Operation	Total
Alive	61	0	61
Dead	0	1*	1
Untraced	0	2	2
Total	61 (95%)	3	64

*Moribund on admission.

TABLE VI

CONDITION OF 61 SURVIVORS AFTER TREATMENT OF SIMPLE MENINGOCOELE

No deformity or paralysis	48
Minor weakness of limbs	9*
Impaired sphincter control	4
	61

*Includes three cases of diastematomyelia with bony spur.

To attempt an estimate of the chance of survival of a child suffering from myelomeningocoele is far from easy, because so many different factors have to be considered, and the data presented in Table VII must be interpreted with caution. An attempt has been made in this table to classify the causes of death

TABLE VII

FATE OF ALL CHILDREN WITH MYELOMENINGOCOELE

	Operation	No Operation	Total
Alive	95	8	103
Died of hydrocephalus	27	36	63
Died of meningitis	3	29	32
Died of other or uncertain causes	9	28	37
Untraced	2	6	8
Total	136	107	243
Survival rate	70%	7·5%	43%

in these cases, but most of the patients for whom operation was not advised passed out of our care and many of them died at home. As a result, the certified cause of death is somewhat imprecise in many instances. For example, a considerable number of the patients are said to have died of bronchopneumonia, and it is likely that this diagnosis has been used to cover those cases with established hydrocephalus in which the end came by way of medullary failure. Moreover, although the percentage of survival after operation on the spine is so much higher than that which ensues when no operation is advised, it must be remembered that many of the rejected patients were feeble, and even moribund, when first seen. What emerges clearly is that the risk of meningitis is greatly diminished if the spinal defect is repaired and the cerebrospinal fluid pathways sealed off.

The total mortality figures for all children suffering from myelomeningocoele have been further broken down in order to ascertain the degree to which the development of hydrocephalus affects the eventual prognosis. It was surprising, and somewhat gratifying, to find that when this complication does not arise, the survival rate is as high for children with myelomeningocoele as for those with simple meningocoele (Table VIII). The role of surgical

TABLE VIII

FATE OF CHILDREN SUFFERING FROM MYELOMENINGOCOELE WITHOUT HYDROCEPHALUS

	No Operation	Operation	Totals
Alive	3	55	58
Died of meningitis	14	2	16
Died of other or uncertain causes	7	1	8
Untraced	2	0	2
Totals	26	58	84
Survival rate	12%	95%	69%

repair in preventing meningitis is clearly seen in this table also. But although the preservation of life is in itself important, some regard must also be paid to the condition of those whose life is prolonged by surgical treatment. Here, Table IX gives some

TABLE IX

CONDITION OF 55 SURVIVORS AFTER TREATMENT OF MYELOMENINGOCOELE WITHOUT HYDROCEPHALUS

No deformity or paralysis	25
Minor deformity or weakness of limbs	7
Sphincter paralysis, limbs normal or with minor weakness	8
Sphincter paralysis, legs paralysed below knees	6
Total paraplegia	7
Epilepsy	1
Insufficient information	1
	55

ground for optimism. Of the 55 survivors, 32 (58%) are alive and well. Those who can walk, with or without the aid of callipers, but who are incontinent, and one suffering from epilepsy though not from spinal paralysis, we would classify as disabled, and these amount to 15 cases (27%). Seven patients (13%) are suffering from total paraplegia, though their survival is not without enjoyment to themselves and to their relations because none of them presents any mental defect.

Myelomeningocoele with hydrocephalus carries, of course, the most serious prognosis of any group of cases in this study. But even in these gravely deformed children, the outlook is not entirely hopeless. Table X shows once again that repair of the

TABLE X

FATE OF CHILDREN SUFFERING FROM MYELOMENINGOCOELE WITH HYDROCEPHALUS

	Hydrocephalus		No Operation	Total
	Pre-operation	Post-operation		
Alive	20	20	5	45
Died of hydrocephalus	10	17†	36*	63
Died of meningitis	1	0	15	16
Died of other or uncertain causes	4	4	21	29
Untraced	1	1	4	6
Total	36	42	81	159
Survival rate	56%	48%	6%	28%

†Acute post-operative, 1 case
*Acute post-operative, 5 cases

spinal defect is essential if only to reduce the risk of death from meningitis and, as has been remarked in an earlier section of this paper, gives no ground for the supposition that operation plays any important part in determining the onset of hydrocephalus. There is also no evidence that it made any difference to the outcome whether hydrocephalus was already present before the operation on the spine, or only developed thereafter. Table X also makes it plain that the overall risk of some degree of hydrocephalus —not necessarily fatal or disabling—in all cases of myelomeningocoele is considerably in excess of the figure of 50% which is usually quoted. Of 242

TABLE XI

CONDITION OF 40 SURVIVORS AFTER TREATMENT OF MYELOMENINGOCOELE WITH HYDROCEPHALUS

	Mentally Normal	Backward
No deformity or paralysis	8	2
Minor weakness of limbs	4	2
Limbs normal or with minor weakness, sphincter paralysed	7	1
Below-knee and sphincter paralysis	3	—
Total paraplegia	7	6
	29	11

patients, only 84 showed no evidence of hydrocephalus at any time, as compared with 158 in whom this complication was observed. The incidence of hydrocephalus was therefore 65%. It is of course in the hydrocephalic survivors that the problem of mental defect and epilepsy becomes important, but Table XI shows that of all cases of myelomeningocoele with hydrocephalus in which the latter has been arrested either spontaneously or with the aid of surgery, to the extent that it is no longer fatal, not more than 27·5% have become mentally crippled. We have taken as our arbitrary standard of backwardness an intelligence quotient of less than 80, a figure which is generally held to be barely compatible with normal schooling. Improvements in the surgical treatment of hydrocephalus, which have indeed been occurring throughout the period of this study, may reduce the risk still further in future series of cases. There is only one among the 11 surviving backward and hydrocephalic children in whom the size of the head is not grotesquely large, and in this child there was a long episode of suppurative ventriculitis and meningitis after operation, hence it is fair to conclude that the intellectual deficit, in this single case of arrested hydrocephalus with mental defect, results not from any congenital malformation of the brain but from the effects of ill-controlled intracranial infection.

There were, then, 40 children who have survived at least two and a half years, and considerably longer in many cases, despite the twin handicaps of myelomeningocoele and hydrocephalus. Of these, 12, or 30%, of all survivors are to all intents and purposes normal. Ten, or 25%, can walk but are disabled by incontinence; seven, or 17·5%, are totally crippled by paraplegia. Of the 11 mentally backward cases, five are ambulant, and therefore can take some part in the life of an institution for the care of mental defectives. The remaining six children, totally crippled in mind and body, present a pitiable spectacle, but one which should not engage an undue amount of attention, forming, as it does, only a small fraction (six out of 243 cases, or 2·5%) of the total picture.

Discussion

The main purpose of this communication is to describe in terms of the chance and quality of survival the results which have been obtained in the treatment of spina bifida cystica of all grades of severity carried out in the neurosurgical unit of a children's hospital. Whatever the conclusions which can be drawn from these results, it would be wrong to suggest that they must necessarily form the basis of assessment for treatment by all neurosurgeons in all countries. In deciding his attitude to the problem of spina bifida cystica, the neurosurgeon must obviously consider first the conflicting claims of all the various types of disorder, both congenital and acquired, in adults as well as in infants and children, with which he is called upon to deal, together with the resources in terms of hospital beds, operating time and the like, to which he has access. There is also the question of whether it is likely that adequate aftercare, both from the medical and from the social point of view, can be provided for children with varying degrees of physical, and possibly mental, handicap. The prospects of this will undoubtedly vary considerably between countries, perhaps from industrial to rural areas in the same country, according to the attitudes and financial status of the parents, and to some extent to the size and potential helpfulness of the family unit.

Leaving aside these wider social implications, it is clear that the problems inherent in the management of a case of spina bifida cystica fall under three main headings, each of which must be separately considered.

Associated Malformations of the Brain Including Hydrocephalus.—This problem hardly arises in cases of simple meningocoele. Encephalo-cranial disproportion seems rarely to occur in these cases, and there is no evidence in our results that hydrocephalus is a common or serious complication. In myelomeningocoele, however, the association of encephalo-cranial disproportion is almost invariable and the fact that the whole central nervous system is so grossly and diffusely deformed might lead one to suppose that it was also incapable of normal function at all levels. This is by no means the case. The fact that less than 30% of the surviving cases of myelomeningocoele with hydrocephalus show evidence of mental retardation or epilepsy shows that whatever its macroscopical appearance, the brain in encephalo-cranial disproportion is capable of normal function as the organ of mind. One may therefore conclude that if hydrocephalus can be arrested at a reasonable level, then an attempt to achieve this is justified in terms of the eventual mental status of the child.

Meningitis.—By far the most important factor in preventing this complication is the repair of the spinal defect, though of course it hardly exists—except as a rare and regrettable complication of operation—in cases where the cystic swelling is soundly epithelialized from the time of birth onwards. It has already been pointed out that actual rupture of the sac is an indication for immediate operation if life is to be saved. But the commoner state of affairs is that which is seen in cases of myelocoele where the infant is born with an area of exposed neural tissue in the mid-line of the back. Such a case poses something of a surgical dilemma. Mention has been made above of the fact that operation in the neonatal period may cause some deterioration in the amount of active movement in the legs although the operator is not conscious of inflicting any serious degree of trauma upon the exposed cord. On the other hand, while the cord remains devoid of an adequate covering of skin, it is certain to become infected to a greater or lesser extent, though operation is technically simpler and the viability of the infant easier to assess if the repair is postponed to at least the age of 3 months. If adequate medical supervision is available, it is usually possible to induce epithelialization of the bare area without any inward spread of infection, and attention has been already called to one case in which even an actual chronic escape of cerebrospinal fluid over a period of years has not been followed by meningitis. Long before the advent of the antibotic era, 'spontaneous cure' of a myelomeningocoele by cicatrization was known to be possible and not infrequent.

Paraplegia.—With modern advances in the treatment of paraplegia, the prospect of survival of a patient who is paralysed at a lower level than the tenth thoracic segment of the cord is by no means bad. Most of the children in this series who have survived beyond the age of 5 years in a state of paraplegia have, in most cases, developed bed sores at one time or another. But a period of hospital care has been successful in healing these, and there have been no fatalities from this complication. It might perhaps have been expected that infection of the urinary tract and renal lithiasis would have proved a more serious cause of death. No conclusive evidence can be presented upon this point, because there is a group of 37 infants and children who are known to have died but in whom the cause of death was not definitely established as due either to hydrocephalus or meningitis. Of these, only two in the operated and one in the unoperated series are definitely known to have died of urinary infection. There were five deaths from gastro-enteritis and in most of the others the cause of death was certified as bronchopneumonia. As against this, there are 44 survivors in the operated group, and eight in the unoperated group, in all of whom there is lack of voluntary control of the bladder. About half of these children have survived for periods of more than five years, and several have had at least one episode of urinary infection, but in every instance it has been controlled by medical means in the first instance, combined in a few girls with the creation of an ileal-loop bladder. The impression which one gains from these figures is that as in the case of paraplegic adults, urinary infection, though it needs constant careful attention, is no longer the fatal condition that it used to be. But an even longer period of follow-up is necessary to obtain definite information about this.

Mention has already been made of the fact that the criteria by which children were accepted or rejected for repair of the spinal defect varied from time to time during the period of this study. A retrospective survey of our case material suggests that there were times when an unduly pessimistic view was taken of the outcome in cases of myelomeningocoele with some degree of hydrocephalus and a more or less complete paraplegia, and the fact that eight patients who had been regarded as hopeless have none the less survived for more than two and a half years would seem to confirm this impression. If this is correct, and if one makes the further assumption, which seems justified in the light of recent advances, that the number of deaths from hydrocephalus can be halved by the appropriate surgical treatment, then the chance of worthwhile survival of all infants born with myelomeningocoele, of whatever grade of severity, is of the order of 60%, and slightly better in males than in females.

It is interesting to compare the data presented in this paper with those given by Ingraham and Swan (1943). The number of untraced cases was larger in their series than in ours (61 out of 462 or 13·2% as against our 10 out of 307 cases or 3·3%) and is disregarded in their estimates of mortality, while in considering the more serious forms of spina bifida, we have made the arbitrary, but probably justified, assumption that all untraced cases are dead. Ingraham and Swan judged that 208 out of their 401 traced cases of spina bifida, including simple meningocoele, that is to say 52%, were suitable for operation: we operated upon 197 out of 307 or 64% and believe that the proportion might justifiably be increased still further in the future. Disregarding untraced cases in both series, it seems that Ingraham and Swan had 160 survivors out of 200 patients submitted to operation while we had 156 out of 197. The survival rate in the two series is almost identical.

Finally, Ingraham and Swan considered in the light of their experience that 30% of patients with spina bifida could look forward to a life unhampered by any significant incapacity; our series yields the very similar estimate of 101 out of 307 cases or 33%. The conclusion which we would draw from this comparison is that while the technique of surgical repair of spina bifida cystica itself has shown, and is probably capable of, no great improvement, there are advances in other fields, such as the surgical control of hydrocephalus and the care of the crippled, which should tend to an improvement in the overall likelihood and duration of survival, and which should lead in the future to a decreasing proportion of infants with spina bifida cystica being left to the death which, without surgical help, so frequently awaits them.

Summary and Conclusions

This communication studies a series of 307 consecutive personal cases of spina bifida seen during a 10-year period. Of these, 96·7% have been traced and the minimum period of follow-up of the survivors is two and a half years.

Spina bifida cystica is a more serious condition in females than in males. Only 50% of all female infants with myelomeningocoele were judged fit for operation on the basis of degree of neurological deficit and of hydrocephalus as against 63% of males. Of all female cases of myelomeningocoele, whether operated upon or not, 40% survived as against 46% of males.

The timing of the surgical repair of the spinal defect is discussed and the operative technique described. Routine operation in the first few days of life seems to present no significant advantage. Repair of the spinal defect does, however, greatly reduce the risk of death from meningitis and brings no real additional risk of hydrocephalus. It rarely causes any deterioration in neurological status. One hundred and ninety-seven, or 64%, of the patients in this series were deemed fit for operation on the spinal defect, and of these, 156 (79%) survived.

The occurrence of hydrocephalus in cases of spina bifida cystica is almost invariably associated with an extensive malformation of the hind brain hitherto known as the Arnold-Chiari malformation. In the light of recent work on the pathogenesis of this condition, it is suggested that it be known as 'encephalocranial disproportion'. Despite the abnormalities in structure of the brain in encephalo-cranial disproportion there is no evidence that the condition is in itself incompatible with normal intellectual status. On the contrary, if the hydrocephalus is arrested either spontaneously or by surgical means, the ultimate intellectual status of the majority of survivors is normal. Of the 156 known survivors in this series, 33% show no significant neurological disability and more than half of the remainder are mainly handicapped by incontinence. Almost every child who has any power in the proximal muscle groups of the legs can eventually be enabled to walk with the appropriate orthopaedic assistance, either by way of operation or by the provision of suitable appliances.

There are 20 patients with total paraplegia still alive, and investigation into their present status suggests that further long-term survival is not unlikely. While episodes of urinary infection and especially of the appearance of bed-sores have occurred in the majority of cases, they have proved amenable to treatment in hospital, and of the paraplegic infants and children who have not survived, only three are known to have died of urinary infection, and none of the effects of bed-sores.

In the light of these findings, it can be argued that the most important remaining limit to the number of infants born with spina bifida cystica of all grades of severity who can live a worthwhile, even if restricted, life, is the amount of medical and surgical care which can be expended upon them.

This study has been made possible by the action of the Manchester Regional Hospital Board in creating a special appointment as research assistant for one of us (P.A.D.) from 1959 to 1960.

We gladly acknowledge the help of many of our colleagues at the Royal Manchester Children's Hospital in the medical and surgical care of the children reported in this paper, particularly that of Mr. W. Sayle-Creer and Mr. D. D. Cranna, consultant orthopaedic surgeons, and of Mr. D. S. Poole-Wilson and Mr. A. A. Ashworth, consultant genito-urinary surgeons.

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THE PROGNOSIS OF SURVIVAL FROM CEREBROVASCULAR ACCIDENTS

BY

IAN D. MELVILLE and STEWART RENFREW

From the Royal Infirmary, Glasgow

No longer can a physician remain passive towards a patient who has presented with a cerebrovascular accident, for an intracerebral haematoma is now an operable condition. Moreover a haematoma may be a more common cause of slowly attacking strokes than has been previously thought. Arteriography, which is often a diagnostic necessity, and operation itself, however, are not without risk (Baker, 1960; Bull, Marshall, and Shaw, 1960; McDowell, Schick, Frederick, and Dunbar, 1959; Sedzimir, 1960). The clinician is, therefore, faced with the problem of advising these procedures in patients who are not dying but may die as a result of them.

Were it possible to predict death or survival in the early stages of a cerebrovascular accident, this problem would be solved, for, if it is confidently predicted that a patient is going to die, the physician is free to do nothing or to carry out any treatment no matter how heroic. On the other hand, if it is predicted with confidence that a patient will survive, then the physician must be sure that any potentially dangerous investigation or operation, now no longer excusable as life-saving, must offer substantial benefit in terms of reduction of ultimate disability.

The purpose of our investigation was to discover early clinical and E.E.G. evidence which would allow confident predictions of life and death in cerebrovascular accidents. As far as we are aware, such predictions are not possible on the basis of present knowledge.

Material

The patients in our series were confined to those who were seen during 1960 and who were examined within seven days of the onset of the stroke. The total number of patients examined was 96 but six were excluded because they were considered to have brain-stem lesions. The series, in fact, contains only those patients who were thought to have cerebral infarctions or intracerebral haematoma. A further five patients were excluded since they had convulsions, on the grounds that such seizures may produce alterations in consciousness and also muscular weakness. Such postictal features confuse the clinical picture of a stroke and of course produce E.E.G. abnormalities which are not directly relevant to the cerebrovascular accident itself. The series to be reported, therefore, consists of 85 patients.

The age distribution of the patients was as follows.

Decade	4th	5th	6th	7th	8th	9th
Number	2	14	23	28	14	4

The time intervals between the onset of the strokes and our examinations were as follows.

	Days						
Interval	Under 1	1-2	2-3	3-4	4-5	5-6	6-7
Number	39	19	5	12	3	3	4

Methods

Each patient had a detailed neurological examination and 79 had an E.E.G. Twenty-five patients had the cerebrospinal fluid examined, six had neurosurgical operations, and 31 of the 43 fatal cases had necropsies. In the clinical examination particular attention was paid to the level of consciousness and to the severity of the hemiplegia.

The grading of the level of consciousness is one commonly used and is shown in Table I. Most patients were not seen within 12 hours of the onset of the stroke and it follows that all the gradings of conscious levels given in our results refer to examinations made after 12 hours. A few patients who were seen under 12 hours were not

TABLE I

GRADING OF CONSCIOUS LEVELS

Grade of Consciousness	Clinical Assesment
1	No response to any stimulus
2	Response to painful stimulus only
3	If aphasic, performs simple acts spontaneously, *e.g.*, feeding, adjusting blankets, or simple imitative movements If not aphasic, obeys simple commands, *e.g.*, closing eyes, raising hand
4	If aphasic, performs complex acts spontaneously, *e.g.*, personal toilet, or complex imitative movements as in neurological examination If not aphasic, obeys complex commands as in a neurological examination

graded until a 12-hour period had elapsed, unless death occurred before this. No patients, as far as we could judge, deteriorated in their conscious level from 3 to 2 (a critical change as will later be seen) between the onset and the time of our examination. Hence, conscious level 1 or 2 in the tables of results implies a persistence of these levels for at least 12 hours, unless, of course, death supervened. However, on the basis of observations by general practitioners and house physicians, several patients evidently improved from conscious levels 1 or 2 to levels 3 or 4 before we saw them. Again as far as we could judge, the duration of levels 1 and 2 was short, usually an hour or so and certainly well within the period of 12 hours.

In the assessment of hemiplegia we distinguished between (*a*) a hemiplegia consisting of complete paralysis of all parts on one side and (*b*) a hemiplegia consisting of either complete paralysis of some parts or of incomplete paralysis of all parts on one side. Henceforth type (*a*) will be called a total hemiplegia and type (*b*) a partial hemiplegia. No attempt was made to grade the hemiplegia in patients who had a conscious level of 1 or 2.

Electroencephalograms were recorded immediately after the clinical examination on either an eight-channel Ediswan or a portable Offner apparatus. Most of the recordings were taken with the latter at the bedside. Bipolar electrodes were used.

The severity of the E.E.G. abnormalities was at first graded as gross, moderate, or slight. The slight abnormalities were those which are occasionally found in normal people, whereas the other abnormalities were outside normal limits. To simplify the tables grossly and moderately abnormal records were grouped together and called grossly abnormal. The slightly abnormal records were grouped with the normal records. Grossly abnormal records were divided into those which showed bilateral abnormalities and those in which the abnormalities were confined to one side.

Some E.E.G.s showed a loss of activity in parts of the cerebrum but this feature was ignored in favour of high-voltage slow waves. In two patients, however, a total loss of activity, which was clearly related to their moribund state, was considered to be grossly abnormal.

Results

The mortality rate for the series was 52%. All deaths were considered to be attributable to the strokes. Diagnosis was verified in 45 of the 85 cases and Table II shows the distribution of the various pathologies and mortality. An arteriogram showing a blocked vessel was taken to be diagnostic of a cerebral infarction. Infarction, however, was not diagnosed in patients with normal arteriograms since a normal arteriogram may equally well be found with an intracerebral haematoma (Bull *et al.*, 1960; McKissock, Richardson, and Walsh, 1959). In the presence of a normal arteriogram, therefore, the diagnosis was left open.

TABLE II

CORRELATION OF PATHOLOGY AND MORTALITY

	Verified Haematoma	Infarction (Thrombosis)	Infarction (Embolism)	Diagnosis Uncertain
Alive	2	4	4	32
Dead	14	17	4	8

Relation of Mortality to Conscious Level and Severity of Hemiplegia.—Table III shows a mortality of nearly 100% in patients who presented with conscious levels 1 and 2 persisting for at least 12 hours. The survivor in this group was a woman who was operated on four days after the development of a slow-onset hemiplegia. By the time she was seen she was moribund, but evacuation of a large intracerebral haematoma was followed by marked improvement, leaving her eventually with only a speech deficit. With conscious level 3 survival and death occurred in nearly equal numbers. With conscious level 4 there was no mortality.

TABLE III

CORRELATION OF MORTALITY, CONSCIOUS LEVEL, AND SEVERITY OF HEMIPLEGIA

Conscious Levels	1 and 2	3		4	
Severity of Hemiplegia		Total	Partial	Total	Partial
Alive	1	5	8	2	26
Dead	28	10	5	nil	nil

Severity of hemiplegia was not measured in patients with conscious levels 1 and 2. At conscious level 4 all patients survived irrespective of the severity of the hemiplegia. At conscious level 3, however, total hemiplegia carried a 67% mortality and partial hemiplegia a 38% mortality.

Relation of Mortality to E.E.G.s.—Of the 85 patients, 79 had E.E.G.s. Table IV shows that the occurrence of bilateral gross abnormalities was associated with a mortality of 90% whereas the mortality with any other kind of E.E.G. was only 5% and with a normal E.E.G. it was nil.

TABLE IV

CORRELATION OF MORTALITY AND E.E.G.

	Grossly Abnormal E.E.G.		Normal E.E.G.
	Bilateral	Unilateral	
Alive	4	21	15
Dead	37	2	—

Relation of Mortality to Clinical State and E.E.G.—Table V correlates conscious levels 1, 2, and 4, E.E.G.s, and mortality.

At conscious levels 1 and 2 bilateral gross E.E.G. abnormalities were related to death in all patients except one who has already been mentioned. Two

TABLE V

CORRELATION OF MORTALITY, CONSCIOUS LEVELS 1, 2, AND 4, AND E.E.G.

E.E.G.	Conscious Levels			
	1 and 2		4	
	Alive	Dead	Alive	Dead
Bilateral gross	1	23	—	—
Unilateral gross	—	1	13	—
Normal	—	1	13	—
No E.E.G.	—	3	2	—

patients in this group did not have these gross abnormalities.

At conscious level 4, on the other hand, no patient had bilateral gross abnormalities and all the E.E.G.s showed either unilateral gross abnormalities or no abnormalities.

Table VI shows the correlation between total and partial hemiplegia at conscious level 3, mortality, and E.E.G.s. With regard to cases of total hemiplegia, eight out of 10 showing bilateral gross

TABLE VI

CORRELATION OF MORTALITY AND SEVERITY OF HEMIPLEGIA WITH CONSCIOUS LEVEL 3 AND E.E.G.

	Severity of Hemiplegia			
	Total		Partial	
E.E.G.	Alive	Dead	Alive	Dead
Bilateral gross	2	8	1	5
Unilateral gross	3	1*	5	—
Normal	—	—	2	—
No E.E.G.	—	1	—	—

*At necropsy on this patient, who had a hemiplegia and aphasia no cerebral abnormality was found.

abnormalities died. Of four patients with unilateral E.E.G. abnormalities (there were no normal E.E.G.s), only one died. The E.E.G., therefore divided this group, previously seen to have a mortality rate of 67% (Table III), into two subgroups one of which had a relatively high mortality rate of 80% and the other a relatively low mortality rate of 25%.

With regard to cases of partial hemiplegia, five out of six with bilateral gross abnormalities died, whereas five with unilateral abnormalities and two with normal E.E.G.s all survived. Table III showed that the mortality rate of this group was 38% but the E.E.G. is now seen to divide the group into two subgroups, one of which had a relatively high mortality rate of 83% and the other which had no mortality.

Discussion

It is clear from the results that a confident prediction of life and death can be made from conscious levels 4 and 1 and 2 respectively, provided the last two persist for at least 12 hours. Although the E.E.G. correlates well with the prognosis it is obviously superfluous as a prognostic aid unless the physician has some doubt about the level of consciousness. With conscious level 3, however, the situation is rather different. Even with the additional information of the severity of the hemiplegia, the predictions of life and death are not sufficiently accurate for clinical purposes. It is here that the E.E.G. proves useful, for a distinction between bilateral gross abnormalities on the one hand and other kinds of E.E.G.s on the other allows highly accurate predictions of death and survival respectively. It may be derived from Table VI that 81% of patients with bilateral gross abnormalities died while 91% of patients with other kinds of E.E.G. survived. It is worth noting that the three survivors, who presented with conscious level 3 and had bilateral gross abnormalities, have remained totally and permanently disabled. A bilateral gross E.E.G. abnormality, therefore, in any patient is an ominous sign.

An important feature of this work is that the predictions were based on clinical and E.E.G. observations and did not depend on the pathology of the cerebrovascular lesions. We admit that many patients with minor strokes can never be confidently diagnosed as suffering from an infarction or haematoma but it does not follow that the immediate prognosis of life and death need be difficult.

Turning to the management of patients with cerebrovascular accidents, we submit that, with respect to those who are doomed, there is no reason for withholding vigorous investigation and treatment since a single survival represents a therapeutic triumph. Such investigations and treatment as arteriogram, ventriculogram, burr holes with needling of the brain, tracheotomy, control of fluid balance and anticoagulants, when indicated, should be undertaken at the earliest possible moment after the onset of the stroke.

The management of patients, whose survival is predicted, requires very careful judgment. The choice lies between making no investigations and pursuing investigations which are potentially disabling, frequently uninformative, and sometimes lethal. Were it possible to predict the degree of the ultimate permanent disability in these survivors the choice might be an easier one. Unfortunately such predictions cannot yet be made, at least with any degree of confidence.

The results of our investigation are not of a kind which bring immediate benefit to the patient or make the physicians' decisions any easier. Indeed, as we have indicated the decisions are made more difficult. Nevertheless, observations on the natural

evolution of cerebrovascular accidents must be accumulated if the assessment of therapy, old and new, is to be given a scientific basis.

Summary

The investigation is reported of 85 patients with either cerebral infarction or intracerebral haematoma studied clinically and by E.E.G. The purpose was to discover evidence which would allow the immediate prognosis for life or death.

It was found that patients fell into three groups: those deeply unconscious who had 100% mortality when treated along orthodox lines; those whose consciousness was not impaired and who invariably survived; and those in an intermediate state of consciousness whose outcome could not be predicted accurately on the basis of conscious level alone. Assessment of the severity of hemiplegia in this group improved the accuracy of prediction to some degree.

The E.E.G was used to divide the last group into two subgroups, one having a high and the other a low mortality.

The implications of this study are clear. Patients who are going to die merit vigorous investigation and treatment. Patients expected to survive must not be exposed injudiciously to possibly dangerous procedures.

Addendum

Since this paper was written, McKissock, Richardson, and Taylor (1961) have indicated in their study of primary intracerebral haemorrhage the prognostic significance of deep unconsciousness 24 hours after onset.

Our findings are in agreement, but in addition, we have found that similar criteria can be applied to cerebral infarction.

We wish to acknowledge the generous help we received from the physicians of the Royal Infirmary, Stobhill Hospital, and Forresthall Hospital, Glasgow, who put their patients and records at our disposal. We also wish to acknowledge the services of the E.E.G. recordists, Mrs. I. Johnson and Miss M. Watson, who not only performed the recordings but also contributed to the clinical observations and E.E.G. analysis.

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INTRAMEDULLARY HAEMANGIOBLASTOMA OF THE SPINAL CORD ASSOCIATED WITH PIAL VARICOSITIES SIMULATING INTRADURAL ANGIOMA

BY

K. R. KRISHNAN and W. THOMAS SMITH

From the Queen Elizabeth Hospital, Birmingham, and the Department of Pathology, University of Birmingham

Intramedullary haemangioblastoma of the spinal cord may be associated with overlying pial varicosities. Wyburn-Mason (1943) referred to 10 cases in the literature and added four of his own. The degree of development of the varicosities is variable but occasionally the cord is completely obscured by abnormal vessels which may give rise to the radiological and operative appearances of intradural venous angioma (Black and Faber, 1935; Wyburn-Mason, cases 53 and 55; Craig and Horrax, 1949). The following case of this type is of practical interest in view of a recent suggestion that more attempts should be made to remove spinal intradural angiomas in order to lessen the dangers of haemorrhage and of cord compression and degeneration (Shephard, 1960).

Case Report

A woman aged 40 was referred to the Neurosurgical Department of the Queen Elizabeth Hospital, Birmingham, in December, 1954, complaining of lumbar pain and paraesthesia, numbness of the left leg, dragging of the left foot while walking, and difficulty in starting micturition. The pain and paraesthesia had been present for seven years and the other symptoms for about two years. Before this she had been in sound health. There was no family history of any similar complaint or of any congenital abnormality.

On examination there was mild spasticity of both lower limbs, bilateral ankle clonus with extensor plantar responses, and sensory loss to pinprick over segments T6 to L1 on both sides and over segments L4 to S1 on the left. Lumbar puncture showed a subarachnoid block and the cerebrospinal fluid protein level was 430 mg./100 ml. Plain radiographs of the spine revealed erosion of the pedicles of the sixth to ninth thoracic vertebrae. Lumbar myelography (using Myodil) showed a long stretch of tortuous vessels outlined by a thin film of contrast medium above the level of T10 and cisternal myelography indicated that the upper limit of the lesion was at T5. A diagnosis of intradural angioma was made, effective excision was considered impractical, and the patient left hospital.

She was re-admitted in May 1960 with complete motor and sensory paraplegia below T10, root pains in segments T8 and T9 on the left, painful flexor spasms, and a distended bladder with dribbling incontinence. Laminectomy was performed exposing segments T6 to T9. A large intradural angiomatous malformation extended upwards, downwards, and laterally beyond the limits of the operative exposure. In an effort to abolish the root pains the left seventh and eighth thoracic sensory roots were exposed and divided, a difficult procedure as they were enveloped in a thick sheath of enlarged vessels. A week later 0·7 ml. of phenol was injected intrathecally as the flexor spasms were still troublesome. After this the spasms were much improved and the patient was able to return home.

She was again admitted in a very much worse state in October 1960 and an attempt was made to excise the lesion. The old laminectomy wound was re-opened and extended to expose segments T4 to T11. The cord was hidden by abundant enlarged and tortuous vessels which extended from the top to the bottom of the exposure, through the intervertebral foramina, and laterally as far as could be seen. Troublesome bleeding was encountered on attempting to define the main vessels and as excision was clearly technically impossible the operation was abandoned.

Post-operatively the patient had an exacerbation of her urinary tract infection and developed severe bronchopneumonia despite active antibiotic therapy. She died three days after the operation from respiratory failure.

Pathological Findings.—Permission was granted only for examination of the spinal cord, which was removed from C3 to L5. Beneath the dura the dorsal and lateral surfaces of the cord between T2 and L2 were covered with a plexiform conglomeration of blood vessels resembling a venous angioma (angioma racemosum venosum). These blood vessels, which gradually became less numerous towards the upper and lower limits of the lesion, were in places obscured by adherent blood clot and gelatin sponge (Fig. 1). Segments T7 and T8 were firm and enlarged. Their cut surfaces (1·7 × 1·4 cm.) were reddish-brown and flecked with irregular yellow areas; dilated blood vessels extended into the cord tissue and the normal markings were not recognizable (Fig. 2B).

FIG. 1

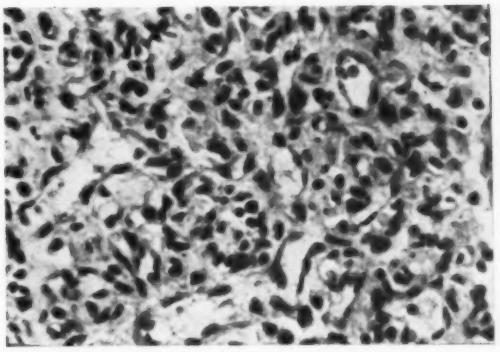

FIG. 3

FIG. 2A

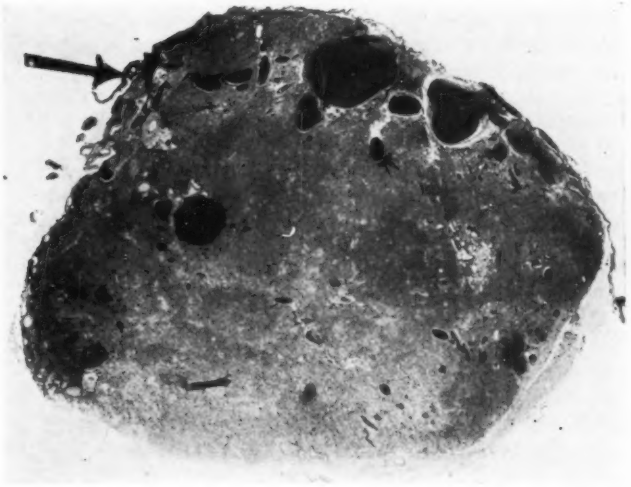

FIG. 4

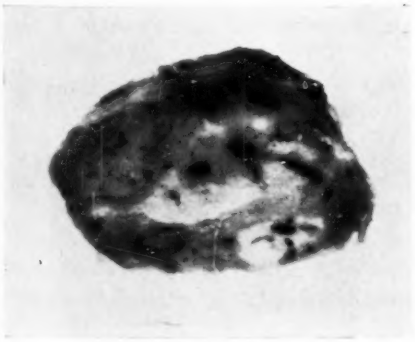

FIG. 2B

FIG. 2C

FIG. 1.—Dorsal surface of spinal cord at T7 - 8 showing dilated pial veins obscured by gelatin sponge and blood clot in the upper part of the figure.

FIG. 2.—A = C8 B = T8. C = T11. Showing syrinx at C8 and T11, tumour at T8, and dorsal pial varices at T8 and T11.

FIG. 3.—T7. Haemangioblastoma. Haematoxylin and eosin × 250.

FIG. 4.—T7. Haemangioblastomatous infiltration replacing normal markings of cord. Note dilated veins. Collapsed veins arrowed. Haematoxylin and eosin × 4·5.

Segments T6 and T9 were shrunken and showed focal softenings. Throughout the rest of the cord in relation to the midline of the dorsal columns was an ovoid, grey area with a central slit-like cavity (Fig. 2A and C).

Histology.—In the enlarged seventh and eighth thoracic segments the normal cord structure is completely replaced by haemangioblastomatous tumour consisting of a network of capillaries, lined by swollen endothelium, and separated by polyhedral stromal cells (Fig. 3) which in some areas are vacuolated and contain sudanophile lipid. The capillaries have a prominent reticulin basement membrane and in places are dilated into larger sinuses. Reticulin fibres enclose and separate the majority of the stromal cells, the nuclei of which sometimes show hypertrophy, hyperchromatism, and/or reduplication.

The conglomeration of surface blood vessels extending from T2 to L2 is composed of dilated pial veins which are most numerous over the tumour and the adjacent shrunken segments, where they also extend into the cord substance (Fig. 4). At the operation site a few pial veins are thrombosed and others are collapsed and covered with gelatin sponge.

The shrunken segments (T6 and T9) adjacent to the tumour show diffuse gliosis and demyelination and areas of recent infarction.

The grey area in the dorsal columns throughout the rest of the cord is a syringomyelic cavity which contains serous fluid and has a dense wall of astrocytic glia in which Rosenthal fibres (see Grcevic and Yates, 1957) are abundant. It is dorsal to the central canal and its relation to the median fissure varies slightly between segments. In places the syrinx involves the dorsal and to a lesser extent the anterior horns, both of which show loss and degeneration of nerve cells and fibres. In the vicinity of the shrunken segments the syrinx loses its cavity and appears in sections as a solid glial trabecula, which divides into two parts before merging with the gliotic segments above and below the tumour.

Discussion

Venous dilatation over a haemangioblastoma of the spinal cord is not unusual but complete covering of the cord by abnormal vessels probably occurs in only a minority of cases. It may be suspected, however, that in the past some lesions described as intradural angiomas from the operative appearances may have been associated with an intramedullary tumour. The cause of the varicosities is obscure: it has been suggested that they are either a secondary result of the tumour or an associated developmental abnormality. According to Wyburn-Mason (1943) varicosities are practically unknown with other varieties of spinal tumour and also with syringomyelia alone.

The association of syringomyelia with haemangioblastoma and other types of intramedullary tumours of the cord is well recognized. The origin of the syrinx in such cases has frequently been discussed (*e.g.*, Russell, 1932; Wyburn-Mason, 1943; Rand and Rand, 1960) and need not be considered here. Varicosities occur most often in those cases of haemangioblastoma in which syringomyelia is also present (Wyburn-Mason).

Before attempting to excise an intradural angioma the possibility that an intramedullary haemangioblastoma may also be present should be considered; operation is contraindicated if this is confirmed. Identification of an associated haemangioblastoma may be difficult. Myelography is not helpful. Ocular and other stigmata of Lindau-von Hippel disease suggest haemangioblastoma. According to Wyburn-Mason the cisternal fluid above an intrinsic haemangioblastoma is frequently xanthochromic and contains very large amounts of protein. But in some cases even operative exploration may fail to disclose the true nature of the condition.

Radiotherapy does not appear to have had a beneficial effect in previously published cases of this association.

Summary

Intrinsic haemangioblastoma of the spinal cord is sometimes associated with extensive pial varicosities which result in the radiological and operative appearances of intradural angioma.

This possibility should be remembered when assessing the operability of an apparent spinal angioma.

An illustrative case is described in which syringomyelia was also present.

We are grateful to Mr. Eric Turner for suggesting that we publish this case and for reading and criticising the manuscript.

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CONTROLLED MULTIFOCAL FRONTAL LEUCOTOMY FOR PSYCHIATRIC ILLNESS

BY

H. J. CROW, R. COOPER, and D. G. PHILLIPS

From the Burden Neurological Institute, and Frenchay Hospital, Bristol

There have been two important developments in the surgical treatment of mental disorders during the last 12 years, and one of these is in the selection of patients. No longer is the chronic schizophrenic the principal type of patient selected for cerebral surgery. The patients now considered for surgical treatment are usually chronic depressives and those with anxiety states, and obsessional syndromes whose symptoms have proved intractable. These cases include young and intelligent people, some with potentially promising futures and many with heavy responsibilities. In such cases it is particularly important to preserve as much as possible of intellectual capacity, sense of responsibility, and social judgment.

The need for more discriminating intervention in cerebral function has been reflected in the variations in operative techniques used in cerebral surgery in recent years. The second important change, then, has been the introduction of methods for the selection and limitation of the site of the destruction so as to do the least damage that will bring significant and prolonged relief of symptoms to the patient. Many attempts have been made to achieve the goal of most relief with least damage. Frontal topectomy was described by Pool (1949), anterior cingulectomy by Whitty, Duffield, Tow, and Cairns (1952), electro-coagulation of limited areas in the thalamic nuclei by Spiegel and Wycis (1949), orbital undercutting by Scoville (1949), frontal electro-coagulation by Grantham (1951), bimedial leucotomy by Greenblatt and Solomon (1952), transorbital leucotomy by Freeman (1948), lower quadrant leucotomy by Thorpe and Hardman (1952), and rostral leucotomy by McKissock (1951).

White, Sweet, and Hackett (1959) have described a method of leaving coagulating electrodes in the frontal lobes of brain for prolonged periods to allow the lesion to be enlarged at a later date if the clinical state indicates the need. They used one or two large electrodes and coagulated by diathermy. This technique was used in cases of intractable pain (usually caused by cancer).

These methods have two limitations: first, however well controlled the lesion is anatomically, they are functionally 'blind' and irreversible; second, being essentially acute operations it is difficult to grade the lesion to match the illness of the patient. Greater delicacy and control of coagulation of frontal white matter can be achieved by using a large number of small, chronically indwelling, intracerebral electrodes.

Technique

Twenty-four to 34 electrodes (4 mm. long, 0·2 mm. diameter) are inserted in each frontal lobe. Those lying in white matter are identified by stimulation. Through each one of these electrodes in turn a small direct current is passed, which causes a temporary suppression of the physiological function of the axons surrounding the electrode, in effect performing a minute, focal, reversible leucotomy. This may be seen as a temporary change in the clinical state of the patient. In this way the potential clinical effect of electrolysis of many small regions can be assessed. The progressive electrolysis of sites thus selected is undertaken over a period of weeks or months until a favourable clinical state has been attained.

Methods

Electrodes.—There are two important factors which determine the choice of electrode material for this method of treatment. The first is electro-chemical inertness. Since the electrodes are to remain implanted in the brain for months, there must be no toxic effects due to the metal. Fischer, Sayre, and Bickford (1957) showed that copper and silver produced local necrosis of brain tissue but that stainless steel was inert. We have found that gold wire is also inert. The second factor to consider is the current-carrying capacity of the electrode. MacIntyre, Bidder, and Rowland (1959) have shown that for small currents the size of an electrolytic lesion (at the anode) is directly related to the quantity of electricity (current × time) passed through the electrode. While the current is flowing through the electrode, considerable erosion of the electrode can take place, especially if the electrode is made from stainless steel (Loucks, Weinberg, and Smith, 1959).

Experiments with various electrode materials *in vitro* have shown that electrodes made from 18/8 stainless

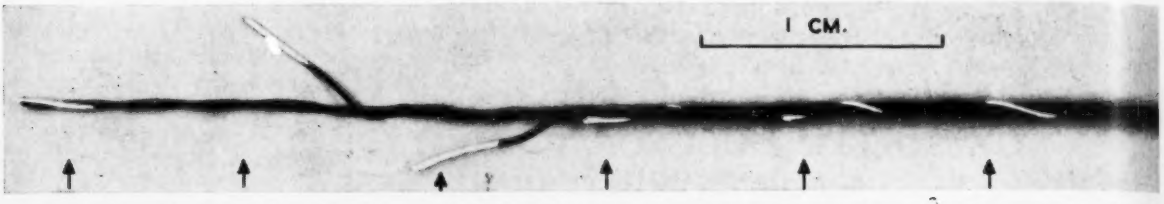

FIG. 1a.—Photograph of electrode sheaf with second and third electrodes from the tip unwound to show how much enamel is taken off.

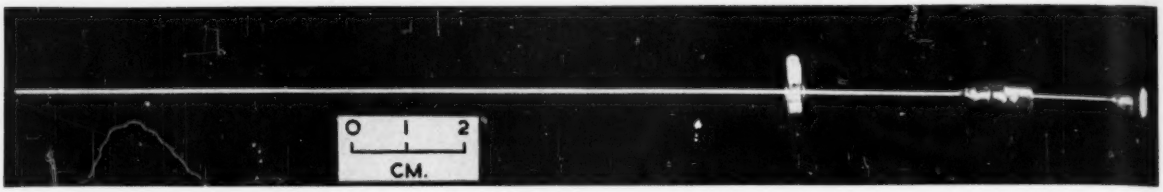

FIG. 1b.—Photograph of introducer needle through which the electrodes are passed. The stillette has been partly withdrawn. The adjustable clip on the needle butts against the stereotaxic frame when the tip of the needle has reached a pre-determined depth in the brain.

steel 0·005 in. diameter (125 μ) with 4 mm. bared will erode away if 10 mA current is passed for 45 seconds (450 milli-coulombs). With 36 gauge (0·0076 in., 190 μ) Staybrite steel wire 10 mA (2400 milli-coulombs) can be passed for four minutes in physiological saline. The size of the lesion produced by a fixed quantity of electricity is also dependent upon the electrode material. MacIntyre *et al.* have shown that for low quantities of electricity (40 milli-coulombs), the volume index in c. mm. (idealized volume of lesion) is 3·1 for gold, 3·1 for copper, 2·4 for silver, 1·3 for platinum, and 0·76 for stainless steel.

The conclusion is that for these purposes the best electrode metal is gold. We are now using 38 gauge (0·006 in., 150μ) fine gold wire insulated with Simgold enamel.* We have found that 10 mA current passed through a standard gold electrode (4 mm. long, about 2 sq. mm. area) for three minutes produces a macroscopic lesion, approximately 5 mm. long and 3 mm. diameter, in fresh cadaver brain. Gold electrodes of these dimensions show negligible signs of erosion. At the time of treatment of some of the patients described in this report, the experiments described above had not been completed and stainless steel, and on one occasion silver, electrodes have been used.

The electrode sheaves are spun on a special instrument, using six gold wires round a stainless steel stiffening wire (36 g.). The gold wires are cut to different lengths so that there are 8 mm. between the tips of neighbouring electrodes and 4 mm. of the insulation is stripped from the end of each gold wire (Fig. 1).

Insertion of Electrodes.—Our technique is based on the method originally used by Dodge, Holman, Sem-Jacobsen, Bickford, and Petersen (1953).

A simple stereotactic frame was built in our workshop, and this has been found to be precise enough for our purpose. The electrodes are introduced, under a general anaesthetic, through bilateral frontal burr holes in the coronal suture, about 3 cm. from the mid-line.

*F. D. Sims Ltd., Ramsbottom, Lancs, England.

Four or five sheaves of electrodes (six in each sheaf) are placed fan-wise in the coronal plane. Originally the fan of electrodes was spread widely in the frontal lobes, just behind the tips of the ventricles, but from experience with the first cases the disposition of the electrode sheaves has been changed so as to narrow the fan and move it backwards into the coronal plane, 0·5 to 1·0 cm. anterior to the anterior clinoids (Figs. 2 and 3).

After the operation the ends of the electrode wires outside the scalp (coded for identification) are soldered to thin insulated tinned copper wires terminated by two 34-way subminiature sockets.† If normal soldering temperatures are used the gold alloys with the solder and disappears into solution. This is prevented by reducing the temperature of the soldering iron to just above the melting point of solder. The sockets are secured to

†Electro-Methods, Stevenage, England.

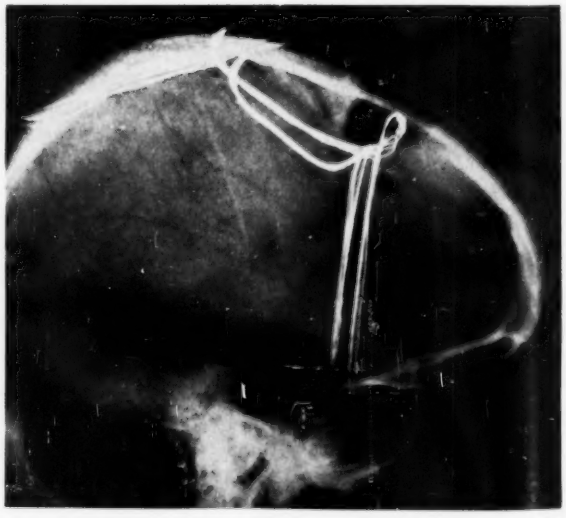

FIG. 2.—Lateral view of the electrode sheaves.

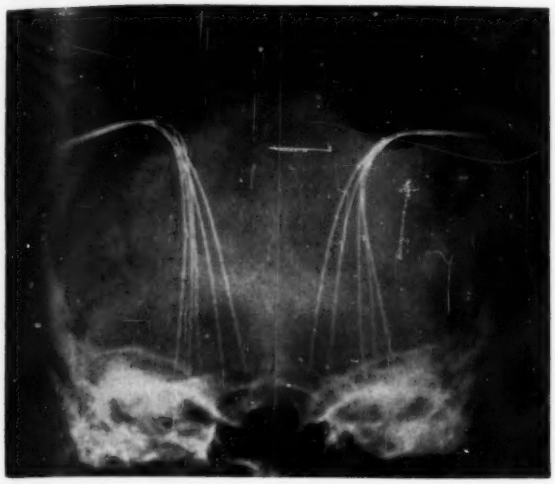

FIG. 3a

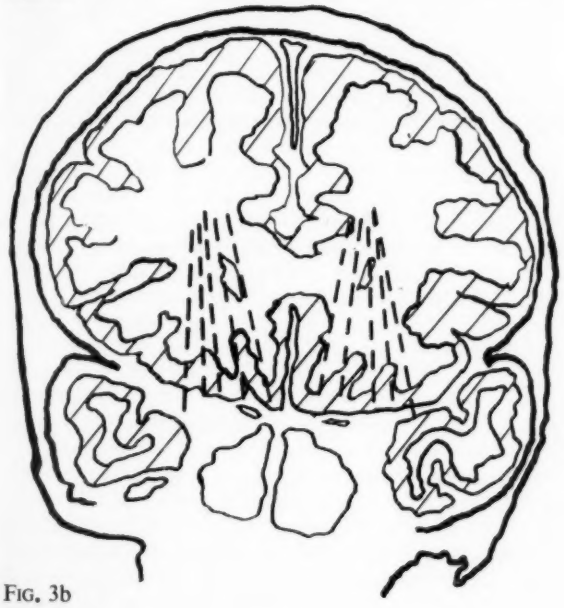

FIG. 3b

FIG. 3a.—Antero-posterior view of the electrode sheaves.
(b) Diagram showing the disposition of the individual electrodes in the brain tissue. The cross hatched portion represents the grey matter.
(The section is taken from *Cranio-Cerebral Topometry in Man* by Delmas and Pertuiset, published by Masson & Cie, Paris, and Blackwell Scientific Publications, Oxford.)

loops of stainless steel wire left in the skull using loops of cotton tape. The electrode wires are taped together with polythene tape, and the bundle fastened to the scalp with surgical strapping. Within three or four days of the operation the patient is up and about. Testing and treatment can be started after about seven days.

Testing and Treatment.—This is done with the patient fully conscious lying on a bed. While testing and treatment are being performed according to a pre-arranged plan, the clinician sits by the bedside talking to the patient, exploring the clinical psychiatric picture, asking for subjective impressions from the patient, and noting any objective changes in the patient's state. Throughout the procedure he holds in his hand a switch which can cut out the passage of all current, if this should seem necessary or desirable (Fig. 5).

Identification of Grey and White Matter.—One of the important advantages of using multiple indwelling electrodes is that lesions can be restricted to white matter, thus avoiding the risk of producing cortical scars which might prove to be epileptogenic. Identification of electrode positions in relation to white and grey matter cannot be achieved by stereotactic control because of the great variation in convolutional pattern between individuals. The fine details of location are best established by functional observations after the electrodes have been in position for some days. In the first cases measurements were made of the passive electric impedance of all the electrodes: this was found to vary from electrode to electrode in a way suggesting that those in grey matter offered a lower impedance than those in white matter. The impedance differences were not very great, however, and a more trustworthy criterion was found to be the propensity of the brain tissue around any particular electrode to develop and sustain an organized after-discharge when stimulated electrically.

Physiological observations have shown that stimulation at cathode electrodes in cortical grey matter can evoke a characteristic local after-discharge above a certain threshold stimulus intensity which is remarkably constant when the other stimulus parameters—stimulation period, pulse duration, and frequency—are fixed (Fig. 4). This is the type 2 after-discharge, defined by Chang (1959) as involving the activity of closely situated neurons. On the other hand, stimulation at electrodes in white matter has no such effect at intensities several times greater than the threshold for grey matter. This effect has been confirmed in our observations: stimulation at electrodes likely to be in frontal white matter has never evoked an after-discharge, while exploration of those in regions likely to be involved in convolutions of grey matter have yielded the patterns of after-discharge distribution to be expected from anatomical diversity (Fig. 3B).

In order to establish the range of variation of electrical threshold in normal cortex a number of measurements have been made of cortical excitability in various regions of the brain in these and other types of patient. With electrodes in sensory, *e.g.*, visual, cortex subjective sensations as well as after-discharges can be used as criteria of response (alterations in oxygen availability have also been found useful in this connexion, see Cooper, Crow, Walter, and Winter, 1961). Using a constant-voltage, *i.e.*, low impedance, stimulator, the threshold for production of an organized local after-discharge in normal cortex is about 4 volts when the pulse width is fixed at 400 μsec. at a pulse rate of 40 per sec. and a stimulation period of 10 seconds. Bipolar stimulation between adjacent electrodes in a sheaf has been used throughout to limit current spread. When electrode pairs in white matter are

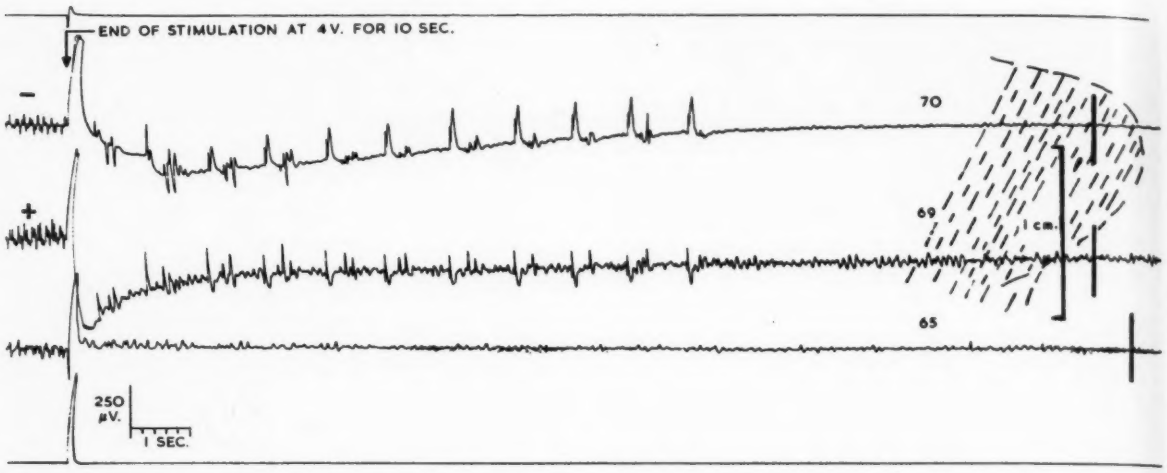

FIG. 4.—Localized after-discharge following stimulation of electrode No. 70 in convolution of grey matter deep in right lateral frontal lobe. Stimulus pulse duration 400 μsec., frequency 40 per sec. The typical rhythm, restriction, and abrupt termination distinguish between electrodes in such regions and those in white matter (electrode 65, channel 3) where stimulation at much higher voltages evokes no after-discharge.

tested, voltages two or three times greater than this produce no after-discharge.

Exploration of the many therapeutic electrodes in the frontal lobes occasionally show after-discharge thresholds of about 8 volts; these are usually adjacent to electrodes showing a lower threshold and are considered to be close to the border between white and grey matter.

Although the waveform and persistence of cortical after-discharges often recall the 'seizure patterns' considered as characteristic of epilepsy in scalp E.E.G. records, this resemblance is misleading since the discharges evoked by focal stimulation involve only very small volumes of cortical tissue—about 0·5 cub. cm.—and the normal intrinsic electrical activity continues unimpeded in regions only a few millimetres away from the stimulating cathode. The extreme restriction of these effects is of considerable physiological interest and importance and is corroborated by the subjective sensations, which are minimal, and often totally absent. Even when electrodes in visual cortex are stimulated, the patients have reported only localized phosphenes, and have not experienced any disturbing sensations.

Using these methods it is possible to chart the functional position of all the electrodes in a few hours, and from this information can be derived a map of the cerebral regions involved showing the distribution of grey sulci which often extend deep into the frontal lobes.

Polarization and Coagulation.—The electrolytic lesions are made using a constant current device similar to that described by Fleming (1957), The direct current can be pre-set to any value from 0 to 20 mA, and the time of rise and fall, to and from this value, is variable from 0 to 60 sec. The electrode around which the lesion has to be made is connected to the positive terminal of the constant current device, and the negative terminal is connected to a large electrode strapped to the forearm.

With the patient fully conscious, and lying comfortably on a bed, low currents (1 mA for 15 sec.) are passed in turn through each of the electrodes lying in frontal white matter. The clinical and physiological state of the patient is observed for some minutes after each polarization. We have found that it is possible to relieve symptoms when certain electrodes are 'polarized' in this way, and that this relief will persist for periods varying from 15 minutes to 24 hours. This temporary relief may be due to very small amounts of permanent damage, with other fibres later taking over the function of those destroyed; or it may be due to temporary electrotonic change in fibres which subsequently recover. After the symptoms have returned, polarization of the same electrode at the same or a slightly higher current value (for the same length of time) will produce temporary relief again. Thus is achieved a reversible focal functional leucotomy.

In order to coagulate the tissue in regions where temporary relief has been obtained, progressively larger quantities of electricity are passed through the electrode. The steps are usually 2 mA for 15 sec., 5 mA for 15 sec., 10 mA. for 60 sec., and finally 20 mA for 180 sec. During the polarization and coagulation sessions the electrocardiogram, psychogalvanic reflex, respiration, and electro-encephalogram from the region being coagulated are recorded continuously. In a session lasting about one hour, up to six electrodes can be treated in this way. Fig. 5 shows the scene immediately after treatment by coagulation of Case 1.

Results

The first five cases treated by this method are now described.

Case 1.—A married woman of 36 had the first of innumerable, unaccountable panic attacks 18 years ago. Twelve years ago she developed an obsessional fear that she would kill her infant daughter. Six years ago she developed an obsessional concept of a stereotyped devil (with horns, tail, and cloak) in her head, telling her to

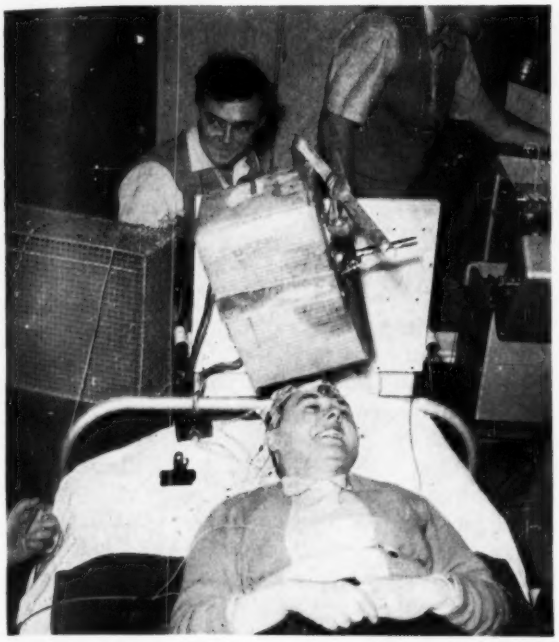

FIG. 5.—Case 1 immediately after the final coagulation of frontal white fibres.

kill her daughter and commit suicide. Although she had insight into the delusory nature of her devil, she was terrified by him. Periodically these symptoms, which were almost constant, drove her to depression and despair. She had had psychotherapy in three hospitals, several courses of E.C.T., and many sedatives and tranquillizers. The only treatment which ever helped was the E.C.T., which relieved only the depression. At the time of operation she had been in hospital for two years, and was quite incapable of leading a normal life.

After the insertion of the intracerebral electrodes, her symptoms of fear and tension were consistently, although temporarily, relieved by polarization of two of the medial electrodes lying about mid-way between the vertex and the floor of the anterior fossa of the skull. Another effect of polarization was to banish the 'devil', but he returned later in modern dress, with a more benign attitude. Coagulation of four points in the frontal lobes produced complete relief of symptoms, and the wires were removed two and a half weeks later.

This remission, however, was shortlived. Within the following 10 weeks she recapitulated the whole complex sequence of events of her 18 years' history of illness. On the assumption that the suppression of abnormal function had been inadequate and in view of the dramatic relief obtained earlier, it was decided to repeat and extend the procedure. A second set of electrodes was inserted in approximately the same position as before. On this occasion the wires were left *in situ* for three months, thus giving a longer period to test the treatment. The lesions were extended and increased in number by stages to eight in each lobe. Again an excellent mental state of calmness without obsessional thoughts or 'devil' resulted. As her symptoms declined, so she acquired a new 'warmth' of feeling for her daughter.

Her condition has steadily improved, and she has now been home for two years living a normal life. There has been no euphoria and no irresponsibility or over-confidence. She has returned to the hospital several times to help and comfort and encourage other patients, and has offered pertinent observations about problems of inter-personal relationships amongst patients in the wards.

Case 2.—A married woman of 60 had a lifelong history of migraine, with a serious functional (hysterical) extension of the pains. Over the years she had had many investigations and treatments. In the last year she had become desperate and suicidal. Electro-convulsive treatment had given only shortlived relief. Electrodes were inserted in the frontal lobes. This patient was treated almost concurrently with the first case. As in the first case, there was an excellent recovery after coagulation in four regions, and the electrodes were removed. But within a few weeks she had relapsed so seriously that an immediate modified 'rostral' type of leucotomy was performed. She has remained quite well in the past two years although she sometimes talks of the head pains.

Case 3.—A married woman of 34 had felt since childhood an obsessional need to think out in detail everything she was going to do, and to consider in detail everything that she had done. If she is interrupted in her prolonged cogitations, which she calls 'my thinks', or is otherwise unable to complete them, she becomes assailed by feelings of guilt and fear. While she was single, she had been able to indulge her obsessional need for 'thinks', by living a slow and simple life. But when a husband, and a home, and then a child were added to her life, she found the day too short for all the necessary 'thinks'. She broke down in a state of terror, exhaustion, and depression. Electro-convulsive therapy relieved the depression but made no difference to the other symptoms. Three stays in hospital were necessary in the 18 months before the insertion of frontal electrodes.

By the time the electrodes were inserted she had been in hospital for some weeks, and in the simple life there, she had lost all her fear and tension. She was calmly performing her daily 'thinks'. Therefore, apart from her 'thinks' she had no symptoms when treatment was being conducted, and the amount of destruction required could not be tested by clinical emotional response.

Sixteen lesions (all smaller than those made in more recent cases) were made in the frontal lobes and the wires were then removed.

She was happy and relaxed, but was indulging in her life-long practice of 'thinks', though she could easily be distracted from them. She seemed to be progressing steadily, if slowly, in abolishing one set of 'thinks' after another. However, after discharge from hospital, she moved into a new house, and the stress of a new set of 'thinks' built up again. She is at present back in hospital, and has severe panics when the 'thinks' are prevented.

This case is a failure. In the light of subsequent experience, not enough damage was done to the

system associating the emotion of fear with conceptualization. This case was treated during the early stages of development when we were over-optimistically conservative about the amount of interference with frontal lobe function needed to relieve such symptoms in patients subjected to continuing social stress.

Case 4.—A widow of 59 had suffered an uninterrupted anxiety-depressive illness for 10 years. She had always reacted to stress with excessive anxiety. During the 10 years of her illness she had had three courses of E.C.T. without significant benefit. She had had stimulant and sedative and tranquillizing drugs. She had been treated by psychotherapy. She had two hospital admissions before leucotomy was offered her.

After treatment by this method of focal frontal leucotomy (eight focal lesions in each frontal lobe) she was completely relieved of her symptoms. We think we did a little too much damage in this case. She lost some intellectual capacity as measured by Wechsler tests, the score dropping from 114 to 109, and the world was a little too 'rosy' for her. But she is fully responsible socially, and considerate of other people's feelings. She has remained very well in the year since treatment.

Case 5.—A fit married man of 46 is intelligent, and, following a course of psychotherapy six years ago, has very good insight. All his life he has been afraid of people, and has lived a secluded personal life, although he became a technical sergeant in the R.A.F., and is married and has two children. His internal tensions and fears had become steadily more intense in recent years, and he finally had to give up work because he could not talk to his colleagues in the office. Drugs failed to help him. There did not seem to be any indication for E.C.T. He was treated by this method (16 focal lesions in each frontal lobe) and has made an excellent recovery. Two months after the withdrawal of the electrodes, he returned to work in the Civil Service. His I.Q., as measured by Wechsler tests, had increased from 122 to 132 after treatment. He has a proper balanced optimism about the future. There has been an increase in the warmth of feeling between him and his wife and children. In the first five months since the treatment, his mental state has steadily improved. The constant feelings of fear and tension disappeared early in his treatment. The abnormalities in his conceptualizing about his relationships with other people in particular with his office colleagues, have subsequently been progressively changing towards normality.

Discussion

At first sight, the method described has certain unfavourable features. Infection is the first obvious danger to consider. This technique for implanting electrodes has been used in several hundreds of cases in America and Europe for a period of seven years. During that time there have been reports of only two cases of meningitis, and one of an infection of unspecified type.

The second danger is the production of unwanted trauma to the brain by the introduction of the electrodes. Trauma, of course, does occur, but no case has been reported where this has produced clinical signs or symptoms or persistent electrical abnormalities. This danger is naturally set against the benefits expected from the procedure. Needless to say, it is less traumatic than the use of the leucotome.

The third danger is the production of toxic lesions in the brain by the metal of the electrodes or by the insulating material on them. The insulating material, an epoxy resin enamel, is extremely inert. The skin of the scalp heals around the insulated electrode wires without any foreign-body inflammatory reaction. Although base metals are toxic, stainless steel and gold are harmless, and gold anodes are not eroded by the passage of current.

The fourth unfavourable feature is the natural reluctance on the part of physicians and patients to produce such an unlikely and unnatural situation as a man walking around with electrodes in his brain for weeks on end, thus rendering himself liable to have his feelings, moods, and thoughts altered merely by plugging the electrodes into a switch box and having a switch depressed. We mention this only to report that it is easy to exaggerate this feature. In practice we have found that our patients have accepted the situation with extraordinary nonchalance. Friends and relatives have also taken it as a matter of course. Other patients in the wards know what is going on but they have not in any way reacted unfavourably. The excellent response of the patients to the treatment, of course, impresses the others, who knew them when all the symptoms were present. So gentle and unfrightening is the whole therapeutic process that other patients have been asking to be treated in the same way (Fig. 5).

Usually the patient, although fully conscious, is unaware of the exact time when polarization or electrolysis has occurred; often he does not know that anything has happened. Sometimes, however, he recognizes a sudden reduction of symptoms and smiles in a relieved way. More often the change of mood during a treatment session is gradual. It may be some considerable time after the mood has changed from anxiety to calmness before the patient is properly aware that a change in himself has occurred although it may have been obvious to the observer.

Immediate side-effects have not been severe and the patients have not been disturbed. Headaches during the passage of the coagulating currents have sometimes been reported. Occasionally peculiar head sensations while the current is passing have been described—'like something moving in my head',

'a crackling noise', 'a squeezed feeling'—but usually the patient talks to the doctor as if nothing unusual were happening.

Delayed side-effects of coagulation have included dull headache during the 24 hours after treatment; nausea some hours after treatment occurred in one case; inattentiveness for some hours up to a few days after treatment has been noticed twice; usually there is a small rise in temperature (0·5 to 1° F.) in the evening after treatment. The patients sometimes sleep for an hour or two later in the day of treatment. Apart from the one case of nausea, all patients remained ambulant, ate meals in the dining room and mixed with other patients in an ordinary way.

When these patients wear suitable headgear, the small plugs of the multiple electrode assembly, which they carry strapped to the crown of the head, are quite invisible. It is therefore possible for them to leave the hospital during the course of treatment. They go shopping and sightseeing and spend week-ends at home or at work. In these ways, the benefits of treatment can be tested by some of the real environmental stresses of the outside world. If the patient reacts to these stresses by, say, build-up of tension and fear, the existing lesions can be enlarged, or the number of lesions can be increased according to the results of the preliminary polarization. In this way the capacity to build up abnormal emotional states can be reduced appropriately.

This method of treatment of serious mental disorder is more time-consuming than many of the current surgical procedures, and at present requires the attention of more skilled persons but it is still in its development stage; with increasing experience more economical procedures are being evolved. Currently, four patients are under treatment at the same time. In any case, the modification of human feelings, thoughts, and behaviour by interference with brain function cannot be considered as a purely economic proposition; delicacy of control and respect for individual needs are of paramount importance.

This procedure for producing focal frontal leucotomy offers certain advantages:

(1) The situation of the electrodes with respect to white and grey matter can be ascertained. This reduces the risk of lesions being made in cortex and hence the likelihood of epilepsy as a complication of treatment.

(2) Selective polarization of the frontal axons at low energy levels produces a discrete focal leucotomy which is clinically and functionally reversible. This is in effect a trial-and-reversible-error leucotomy. If the trial lesions are found to relieve symptoms and not to produce unwanted effects, the lesions can be made permanent by electrolytic coagulation.

(3) The total number of small discrete lesions can be increased, or the lesions enlarged, progressively over a period of many weeks, which may include a probationary period at home and work. This makes possible a more accurate judgment of the minimum amount of destruction required to relieve a particular patient's symptoms in a normal social environment.

In view of the enormous variation in human personality and brain function it is not strange that a brain lesion which gives one mental patient great benefit may not provide relief for another patient. This multiple electrode method of progressive leucotomy provides a tailor-made pattern of brain lesions to suit the individual patient's needs. This requirement is clearly demonstrated by comparing Cases 4 and 5. Case 4 was an elderly, slightly hypertensive woman, whose ventriculogram showed slight frontal atrophy. She was completely relieved after eight focal coagulations in each frontal lobe; this was slightly more damage than she really required, but only slightly more. She lost a little of her intellectual capability, but she is extremely happy—if anything, rather too happy. Case 5, on the other hand, was a fit man of 46. He was relieved of his symptoms, with a significant increase in his intellectual capability, by the production of 16 focal lesions in each frontal lobe. That is, he had twice as much damage produced in the frontal lobes as the elderly woman.

The longest time we have left electrodes in the brain is seven months. This period gives adequate scope for estimating the degree of interference needed for a particular patient, but there is no reason why electrodes should not be left in position longer if the physician thinks it necessary.

During the two years since this procedure was introduced, the results of treatment have been strikingly good in the three successful cases in terms of intellectual capacity, emotional balance, and social adjustment. In the four patients now under treatment, the results are also very promising. The possibility of giving relief from otherwise intractable suffering, and the control that can be exercised over the site and extent of cerebral lesions are the justification for this preliminary report. Now that the technical difficulties have been overcome and the risks of the procedure can be balanced against its advantages, it is intended to test its value more exactingly in a larger selection of patients.

Summary

A method has been developed for obtaining greater precision in the control of the site, size, and duration of lesions in frontal leucotomy. It involves the introduction of large numbers of small, chronically indwelling, gold intracerebral electrodes in the

frontal lobes. A temporary leucotomy can be achieved by electrical polarization of these electrodes; where relief is obtained a permanent selective leucotomy can be performed by electro-coagulation using direct current.

The results in the first five cases are briefly described.

The effects of the procedure can be observed while the patients are leading a normal life as well as in hospital.

No difficulties have been encountered with infection, insertion trauma, or electrode reaction. The patients tolerate the implantation well for periods of several months.

We should like to express our deep appreciation of the encouragement given to us by Professor F. L. Golla, who was the Director of the Burden Neurological Institute when this work was begun.

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INTELLECTUAL IMPAIRMENT IN CHILDREN WITH LOCALIZED POST-INFANTILE CEREBRAL LESIONS

BY

JOHN McFIE

From the National Hospital, Queen Square, London

In the past decade, a considerable amount of evidence has been published demonstrating the association in adult patients between specific intellectual losses and lesions in different parts of the cerebrum. In children, however, well-localized cerebral lesions are relatively rare, and there are few studies of associated intellectual changes; yet an understanding of the relationship of impairment to cerebral damage is of importance both from a theoretical point of view and to enable a full clinical assessment, particularly of prognosis concerning mental development, to be made.

Comprehensive data on patterns of impairment of adult patients on the Wechsler intelligence scales and other intellectual tests have been presented by McFie and Piercy (1952), by Reitan (1959), and by McFie (1960a): detailed studies of the impairment associated with lesions of the frontal lobes have been published by Rylander (1939); of the temporal lobes by Milner (1954, 1958) and by Bingley (1958); and of subcortical nuclei by Riklan, Diller, Weiner, and Cooper (1960) and by McFie (1960b). The intellectual functions typically impaired by lesions in different anatomical lobes are summarized in Table I: perhaps the most significant conclusion which may be drawn from this is that lesions of the left hemisphere are typically associated with verbal impairment, and lesions of the right with losses on performance tests. This has also been emphasized by other authors (Morrow and Mark, 1955; Heilbrun, 1956) and lends no support to the frequent practice of assessing organic intellectual impairment in terms of the 'verbal minus performance' formula.

TABLE I

RESULTS OF TESTS SHOWING SIGNIFICANT MEAN IMPAIRMENT ASSOCIATED WITH LOCALIZED LESIONS (McFIE, 1960a)

Site of Lesion	Tests Showing Impairment
Left frontal	Digit span
Left temporal	Digit span, similarities
Left parietal	Digit span, arithmetic, block designs
Right frontal	Picture arrangement, memory for designs
Right temporal	Picture arrangement, memory for designs
Right parietal	Picture arrangement, memory for designs, block designs

In children, there is evidence that there is a striking difference between the intellectual effects of localized cerebral lesions sustained in the first year of life and in subsequent years. Following the report by Krynauw (1950) that removal of the left hemisphere in infantile hemiplegics resulted in no speech disturbance, a series of studies of patients following hemispherectomy (Cairns and Davidson, 1951; Gardner, Karnosh, McClure, and Gardner, 1955) makes it clear that in cases of injury to either hemisphere at birth or infancy the intellectual functions of both hemispheres are mediated by the undamaged hemisphere alone. McFie (1961a) pointed out that there appeared to be a limit to the intellectual capacity of such patients, the mean I.Q.s of his own series and of reported cases being in the region of 60 points; and also that these patients tended to have lower 'verbal' than 'performance' scores, regardless of which hemisphere had been injured.

In cases of unilateral injury after one year of age, however, the impairment appears to approximate to the conventional adult pattern of verbal deficit with left, and performance deficit with right, hemisphere lesions. This is particularly clear from reports of aphasic children: Karlin (1954) stated that on intelligence tests they show 'a scattered picture, being strikingly backward in verbal tests and showing normal responses in performance tests'. Bryan and Brown (1957), in a study of 40 supposedly 'organic' subjects, stated that 'in contrast to the commonly reported organic pattern, a number of adolescents in the present study had superior performance scores', a conclusion illustrated by a typical case of severe left hemisphere injury at the age of 6 years. These authors also claimed that 'there was a trend for lower full scale I.Q.s to be associated with early brain injury'.

Their subjects whose impairment was present at birth had a mean I.Q. of 62, and in those having infantile injuries it was 66: no other clinical evidence concerning these patients was presented, but the mean figures agree well with other reports. The mean I.Q.s of their subjects injured between 3 and 10 years of age was 71, and of those injured between 10 and 20 years was 85.

In spite of the number of publications on 'cerebral palsy', reports of psychological test results have not generally been concerned with localization or age of onset of the lesion, and results have not been analysed in detail. Thus the extensive account by Taylor (1959) does not attempt to establish any patterns of results for groups, and presents only a few illustrative cases, while Denhoff and Robinault (1960) emphasize the clinical value of Wechsler's children's scale, but repeat the assertion that impairment is likely to be reflected by 'verbal higher than performance' scores. Jewell and Wursten (1952) analysed the results of 166 'cerebral palsied' children tested on the Terman-Merrill scale and 41 on the Wechsler-Bellevue scales, and found that on both scales 'none of these children had vocabulary as his weakest point': this agrees with evidence from testing adults that the vocabulary score is relatively insensitive to cerebral damage. Moreover, the authors found that their subjects were 'twice as likely to have low scores in memory as they were to have high scores'. This applied to both verbal and visual memory, a point of similarity with adult patients. On the Bellevue scale, as many subjects had high verbal I.Q.s as had high performance I.Q.s.

There is suggestive evidence then that the patterns of intellectual impairment in children with post-infantile cerebral injuries approximates to those found in adults. However, just as the symptoms of aphasia may be less obvious in children than in adults (Guttmann, 1942), so the patterns of intellectual impairment may be less precise.

Clinical Material

The patients were all those tested during the last 10 years by the psychologists at the National Hospitals, Queen Square, and Maida Vale, who fulfilled the following criteria: they were between the ages of 5 and 15 years; a unilateral pathological process in the cerebrum began after 1 year of age; the location of the cerebral lesion had been verified either at necropsy or operation, or by air-encephalography, or (in the case of electrical foci with no other abnormal finding) by persistence of a focus at repeated E.E.G. examinations over a period of at least one year. The only patients omitted were those reported as unable or unwilling to cooperate in testing, or those in whom testing was inadequate: there may therefore be a bias towards omission of the more grossly defective or disturbed children. The age at testing and diagnosis of the 40 patients is shown in Table II.

Test Results

The patients were tested either on the Terman-Merrill (1937) and Kohs' (1923) block tests, or on one of the Wechsler scales (Bellevue-Wechsler, 1944; Wechsler, 1949). Five patients fall into both groups, and their results are included with those of both groups.

Intelligence Quotients.—Table III shows the numbers and mean I.Q.s of the patients (on the Terman-Merrill or Wechsler scales) grouped according to site of lesion. For the five patients tested on

TABLE III

NUMBERS AND MEAN I.Q.s OF PATIENTS

Site of Lesion	Number of Patients	Mean I.Q.
Left frontal	4	89·3
Left temporal	11	91·3
Left parietal	12	73·3
Right frontal	2	64·0
Right temporal	6	88·8
Right parietal	5	88·6

TABLE II

AGE AT TESTING AND NATURE OF CEREBRAL LESION OF PATIENTS

Lesions	Age											Totals
	5	6	7	8	9	10	11	12	13	14	15	
Tumours												
Angioma	—	—	—	—	—	—	—	—	2	2	1	5
Meningioma	—	—	—	—	—	—	—	—	1	—	1	2
Astrocytoma	—	—	—	1	2	—	2	—	—	1	1	7
Oligodendroglioma	—	—	—	—	—	—	—	2	—	—	—	2
Abscess	—	—	1	—	—	1	—	—	—	1	—	3
Laceration	1	—	—	—	—	—	—	2	1	—	1	5
Local atrophy	—	—	—	—	1	1	1	—	1	1	1	6
E.E.G. focus	—	—	—	—	2	1	—	2	1	2	2	10
Totals	1	0	1	1	5	3	3	6	6	7	7	40

both tests, only the Wechsler I.Q.s are used. One-way analysis of variance shows that the variation within groups is greater than that between groups, and therefore that the variation attributable to the site of the lesion is not significant.

In view of the claim of Bryan and Brown (1957) that lower I.Q.s were associated with earlier injuries, the patients' I.Q.s were also averaged for groups according to the age of onset of the lesion (Table IV).

TABLE IV

MEAN I.Q.s OF PATIENTS BY AGE OF ONSET OF LESION

Ages (years)	Number	Mean I.Q.
1- 4	5	88·8
5- 9	15	106·0
10-15	20	82·7

The ages at which lacerations, or accidents resulting in atrophic processes, occurred could be determined from the case histories: in cases of tumour and E.E.G. focus, the patients were classified as accurately as possible according to the age of appearance of the first relevant symptom. It will be seen from Table IV that there is no suggestion of a trend associating full I.Q. with age at injury.

Verbal/Performance Differences.—Both the Terman-Merrill and the Kohs' block scales yield only a single measure, designated in both cases as the I.Q. However, the content of the former test is largely verbal, while that of the latter appears to be entirely non-verbal. For the patients who did these tests, a comparison between verbal and performance levels may be made by comparing the two I.Q.s. Table V shows the numbers with left and with right hemisphere lesions whose I.Q.s were lower on the verbal than on the performance tests. While the

TABLE V

ASSOCIATION BETWEEN TYPE OF DEFICIT AND SIDE OF LESION

Lower I.Q. on	Hemisphere Involved	
	Left	Right
Verbal (T-M)	5	3
Performance (K)	2	5

figures do not reach statistical significance ($\chi^2=1{\cdot}6$) it will be seen that there is a tendency for verbal deficit to be associated with left, and performance deficit with right, hemisphere lesions.

Wechsler Subtests—For each subtest of the Wechsler scales, the difference has been calculated between each patient's score and the normal mean at the patient's age. For Bellevue weighted scores, the age means are stated by Wechsler (1944, p. 222): for W.I.S.C. scaled scores the mean at each age is 10 points (Wechsler, 1949). Table VI shows the mean of the 'difference scores' of the patients with lesions in the left and in the right hemisphere. In

TABLE VI

MEANS OF DIFFERENCES BETWEEN PATIENTS' SCALED SCORES AND AGE MEANS ON WECHSLER SUBTESTS

Subtest	Hemisphere Involved			
	Left		Right	
	No.	Mean Score	No.	Mean Score
Digit span	20	−2·9	8	−0·9
Arithmetic	21	−1·4	9	−1·0
Similarities	22	−0·9	8	0·4
Vocabulary	22	−1·8	8	−2·0
Picture completion	21	0·7	9	0·1
Picture arrangement	12	−1·3	6	−3·3
Block designs	22	0·2	8	−0·9
Digit symbol	16	−2·0	9	−4·7

spite of the considerable differences between some of the means for left- and right-sided lesions (*e.g.*, digit span, picture arrangement, and digit symbol tests) none of these is statistically significant, owing to the wide range of variation in individual scores. Nevertheless, it is interesting to compare the direction of differences with those found in adult patients (Table I): with digit span and similarities tests the directions are similar, showing a tendency toward greater deficit with lesions in the left hemisphere; with picture arrangement and block design tests likewise, lower scores being associated with right hemisphere lesions; and also with picture completion, in which there is no mean deficit with lesions in either hemisphere. The greater deficit on the digit symbol test with right hemisphere lesions was not found in adults; and the considerable mean deficit on the vocabulary test with lesions in either hemisphere is altogether different from the findings in adults, who showed no mean deficit on this test with lesions in any location.

Memory for Designs.—This test occurs in the Terman-Merrill scale (1937) and was also given as an isolated test to patients who did the Wechsler scales. The scoring followed the Terman-Merrill criteria, but one and two points were awarded in place of a half and one. The mean scores of patients grouped by site of lesion are shown in Table VII. Not only is the difference between the mean scores of those patients with left and with right hemisphere lesions highly significant ($t=3{\cdot}5$. $P<0{\cdot}01$), but one-way analysis of variance of the six lesions groups

TABLE VII

MEAN SCORES ON MEMORY FOR DESIGNS

Site of Lesion	No.	Mean Score
Left frontal	3	3·3
Left temporal	7	3·4
Left parietal	7	2·7
Right frontal	1	2·0
Right temporal	3	3·0
Right parietal	5	1·8

yields a significant variance ratio ($F=3{\cdot}97$, $p<0{\cdot}05$), indicating an association between the site of lesion and the extent of deficit on this test. These results are similar to those of adult patients, including the finding of greater deficit in the Right Parietal group.

Clinical Disabilities.—Five of the patients with left hemisphere lesions, and none with right hemisphere lesions, were frankly dysphasic: two showed mixed dysphasias, in one the disability was exclusively nominal, and in two it was of the type described by Guttmann (1942), characterized by reduction of speech. Two patients with right-sided lesions, and none with left-sided lesions, showed a degree of disability in constructional and drawing tests that amounted to spatial agnosia. These associations are similar to those found in adults.

Handedness.—Four patients were left-handed, *i.e.*, preferred to use the left hand for writing and other unimanual tasks: three with right hemisphere lesions and one with a left hemisphere lesion. The pattern of impairment, *i.e.*, deficit on verbal or performance tests, of each of these patients was similar to those of the others, that is, to the majority of the right-handed patients with lesions in the same situations. This absence of difference between patterns of impairment of the majority of right- and left-handed patients is also similar to findings with adult patients.

Discussion

The test results of these children fall into two groups: those which are similar to results of testing adult patients with lesions in similar locations, and those which are dissimilar.

In the first group, the closest resemblance to the pattern of impairment usually found in adults is found with the memory for designs test: this shows not only the conventional association of impairment with right hemisphere lesions, but also of greatest deficit with right parietal lesions. There is also a similarity between the children and adult patients in the absence of impairment on the picture completion test. It may therefore be postulated that, within the age range of the patients tested (from 9 to 15 years) the cerebral organization mediating these abilities has become established in adult form. It must be emphasized, however, that these data refer only to children with an English cultural background: in children of other cultures, in whom non-verbal ability is frequently not so advanced (cf. McFie, 1961b), this pattern of impairment might not be found.

A resemblance, though of lesser degree, to adult patterns of impairment is shown in the associations between hemisphere injured and deficit on the digit span, similarities, picture arrangement, and block design tests in the Wechsler scales, and on verbal and performance levels on the Terman-Merrill and Kohs' blocks scales. The failure of any of the differences on these tests to reach statistical significance may be ascribed in part to the relatively small numbers of subjects; but, had they been adults at the time of acquiring lesions, it may confidently be stated that there would have been significant differences, even with these numbers, between groups with right and left hemisphere lesions. It appears that in these children the pattern of cerebral organization mediating these abilities approximates to, but is not yet established in, adult form.

Differences from the pattern of deficit normally found in adult patients are shown in the results of vocabulary and digit symbol tests. The greater deficit on the latter test in the group with right hemisphere lesions may suggest a greater implication of 'right hemisphere functions' in its performance in this age group; but this would have to be confirmed on a larger series of patients. The deficits on vocabulary with lesions in either hemisphere are in agreement with the findings of Hebb (1942), and might suggest that more widespread cerebral regions are concerned in the development of this function in the child than in its later use by the adult. A similar proposal, though with special reference to the prefrontal lobes, has been made by Russell (1959); ' . . . the prefrontal lobes play a specially important part in mental development during the years of learning . . .'

The data concerning the intelligence levels of the patients do not demonstrate any overall differences between groups: they serve, perhaps, to emphasize the paucity of information provided by the single I.Q. The numbers in this group of patients are insufficient, but it would be particularly valuable if a study were undertaken of the patterns of deficit on these tests associated with different ages at testing and also with different ages at which the lesion was acquired.

Summary

Intelligence test results of 40 children with localized cerebral lesions, acquired after the first year of life, are analysed. The association of deficit on the tests with the presence of lesions in certain locations, resembling to a greater or lesser degree the association commonly found in adult patients, is found with performance tests, memory for designs, block designs, picture arrangement (right hemisphere lesions); with verbal tests, digit span, similarities (left hemisphere lesions); and with picture completion (little deficit). It is suggested that the degree to which the pattern of impairment on a test resembles that found in adults reflects the extent of approximation to adult cerebral organization mediating the function.

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PROLONGED ORGANIC PSYCHOSIS WITH RECOVERY IN ADDISON'S DISEASE

BY

SAMUEL I. COHEN and I. M. MARKS

From the Maudsley Hospital, Denmark Hill, London

This case of Addison's disease is unusual in that recovery from hypoglycaemic coma was followed by an organic psychosis lasting two months from which the patient completely recovered with treatment.

Case Report

A 38-year-old housewife was admitted to the London Hospital in coma on August 7, 1960. In 1950 her only child was born, following a mild toxaemia of pregnancy and a prolonged labour. She lactated for eight months. Her periods began again normally but about a year later they became infrequent, and finally ceased in 1953. For four years she had noticed that her skin had been getting darker, and she had had unexplained episodes of headache and vomiting each lasting about a day. These episodes had become more frequent in the four months preceding admission, and during this time she had lost some weight. On the morning of admission her husband had been unable to wake her.

Course in London Hospital.—She was a slightly-built woman, in deep coma, with a generalized deep-brown pigmentation of the skin. There were patches of pigment on the lips and on the buccal mucosa. Axillary and pubic hair were absent. She had marked dental caries. The pulse rate was 100 per minute and the blood pressure 95/60 mm. Hg. The pupils were widely dilated and reacted to light. The limbs showed extensor rigidity with increased tendon reflexes, and the plantar responses were extensor. The blood sugar was 20 mg. per 100 ml.; the plasma contained 140 mEq. sodium, 5·2 mEq. potassium, and 100 mEq. chloride per litre, and the blood urea was 52 mg. per 100 ml. The haemoglobin was 12 g. per 100 ml. Five per cent dextrose was given intravenously by drip, and in half an hour she had recovered consciousness, having then been unconscious for at least 12 hours. For the first 24 hours she was treated with intravenous glucose, saline, and hydrocortisone and then with cortisone and fluorohydrocortisone by mouth. The day after admission the plasma contained 120 mEq. sodium, 5·4 mEq. potassium, 94 mEq. chloride, and 27 mEq. bicarbonate per litre. Over the next four weeks her mood fluctuated between elation and depression; she was at different times muddled, paranoid, and agitated, would sometimes sing loudly in the ward, but at times was apparently normal. The dose of cortisone was gradually reduced from 100 mg. to 25 mg. daily. By September 15 her emotional state was nearer normal and she was discharged home. She was given cortisone 25 mg. and fluorohydrocortisone 0·1 mg. daily. While in hospital she developed a dental abscess and some teeth were extracted. It was thought that dental sepsis might have been a factor precipitating the coma.

For the first week at home her behaviour was very abnormal. She was aggressive, impulsive, demanding, and sometimes offensive; she would interrupt conversations and push to the front of queues. She then behaved in a more normal manner for a few days, and apologized to neighbours whom she had insulted earlier. Following this her behaviour again became abnormal and on September 30 she was readmitted to the London Hospital. She was found to have tonsillitis, which was treated with penicillin. The blood pressure was 100/70 mm. Hg and the plasma electrolytes again showed abnormalities characteristic of Addison's disease. The blood sugar was 100 mg. per 100 ml. on two occasions. She was given cortisone 25 mg. b.d. and fluorohydrocortisone 0·2 mg. b.d. by mouth. Because of continuing disturbed behaviour she could not be managed in a general ward and she was transferred to the Maudsley Hospital on October 5.

Course in Maudsley Hospital.—On admission the physical findings were as before, with a resolving tonsillitis. The blood pressure was 100/60 mm. Hg and she was afebrile. Mentally, she was restless, uncooperative, and strikingly distractible. She was grossly disorientated in time and place. Talk was plentiful and spontaneous; she alternately whispered and shouted, and was often incoherent. The mood was generally flat, with brief spells of tearfulness. She had fleeting delusional ideas largely based on mistaken perceptions, and she frequently misidentified other patients as her relatives. Memory was poor for both recent and remote events, and she was unable to perform simple calculations. The picture was thus typical of an organic confusional state.

For the first four days her condition remained unchanged. Food and drugs were taken with difficulty. The treatment she had been receiving was continued, and when she would not take her drugs by mouth they were given parenterally. The plasma electrolytes were normal. The blood sugar, estimated at random during the day on October 6, was 74 mg. and on October 8, 70 mg. per 100 ml. The fasting blood sugar on October 7

was 52 mg. per 100 ml. An electroencephalogram (E.E.G.) on October 7 showed alpha rhythm at 11 to 12 c/s with a generalized abnormality consisting of an excess of slow and intermediate-slow activity.

From October 8 she was given glucose drinks every two hours. The next day she was less restless, took her food well, and was more rational. On October 10 she was much improved and at times rational. From then on improvement was uninterrupted. Cortisone was continued in the same total dose but from October 10 it was given in three eight-hourly doses. Fluorohydrocortisone was reduced to 0·1 mg. daily. Once she was eating her normal diet, glucose drinks were not given, but a milk drink or some food was given last thing at night and first thing in the morning. By October 17 no intellectual deficiencies could be found and the full-scale Wechsler I.Q. was 116. She was still somewhat emotionally labile, but her mood soon returned to normal and she remained perfectly well. Subsequently, the blood sugar was estimated at varying times on different days, and the lowest value obtained was 97 mg. per 100 ml. On four occasions the blood sugar was estimated after the patient had fasted until 9 a.m., which was much later than she would normally have eaten; the values at these times were 94, 62, 70, and 88 mg. per 100 ml. A glucose tolerance test after recovery was normal.

Two later E.E.G.s showed a gradual improvement, but the abnormality had not completely disappeared on November 14, when she was quite well. In these E.E.G.s photic stimulation elicited a slow wave-and-spike discharge similar to that seen in the E.E.G. of the patient's daughter who is under investigation for a behaviour disorder.

In the nine months that have elapsed since her recovery she has been perfectly well.

Discussion

The presentation of Addison's disease in hypoglycaemic coma is rare. Gittleson (1956) reviewed the literature and reported a case. Neuropsychiatric disturbances have long been recognized as a feature of Addison's disease and they were referred to by Addison in his original description (Addison, 1855). Klippel (1899) described a patient with Addison's disease who developed frequent attacks of incoherence and shouting, sometimes followed by fits, regularly at 4 a.m. He recognized the importance of mental symptoms in Addison's disease, and referred to the '*encéphalopathie addisonienne*'. It seems likely that the cause of his patient's attacks was hypoglycaemia. Woodbury (1958) in a comprehensive review stated that 'it has become increasingly evident that psychological derangements are an integral part of the disease syndrome'.

Our patient's chronic fluctuating organic psychosis was probably the result of a number of factors. First, recovery from hypoglycaemic coma lasting at least 12 hours might be expected to be slow. Secondly, it seems likely that during the patient's first admission and during the period at home her blood sugar level might at times have been abnormally low, although at the times that it happened to be measured it was normal. This is suggested by our finding of low blood sugar values at the time of her admission to the Maudsley Hospital, and by our later observation that the fasting blood sugar could drop as low as 62 mg. per 100 ml. This fluctuating hypoglycaemia might not only have delayed recovery from the initial damage, but also produced symptoms in its own right. Thorn, Koepf, Lewis, and Olsen (1940) have pointed out that symptoms of hypoglycaemia may develop at higher levels of blood sugar in patients with Addison's disease than in normals, and it is known that the E.E.G. of patients with Addison's disease shows a lowered threshold of cerebral reaction to hypoglycaemia (Engel and Margolin, 1942). The mental state in hypoglycaemia may not correlate closely with the blood sugar level at the time, and Fabrykant (1955) has suggested that clinical hypoglycaemic manifestations do not reflect a lowering of the blood sugar *per se* but rather derangements in brain metabolism and function which result from it. Thirdly, the dental sepsis and sore throat are likely to have contributed to the metabolic disturbance. Finally, the abnormality demonstrated in the E.E.G., of the same type as seen in the patient's daughter, although probably incidental, may possibly have increased the sensitivity of this patient's brain to metabolic derangements.

Our patient did not show any of the usual symptoms of hypoglycaemia, such as hunger or sweating, and in fact the only symptoms of it were mental. In patients with Addison's disease and psychiatric symptoms, it would thus seem important to consider whether chronic hypoglycaemia might not be the cause of the mental disturbance. This could be the case even though the blood sugar level is normal at the time of the disturbance, and it may also be possible that levels of blood sugar which are ordinarily considered normal are inadequate for the nutrition of the brain of the patient with Addison's disease. A therapeutic régime on the lines we adopted might be worth trying in such cases.

The prolonged confusional state in our case closely resembles that described by Blau and Hinton (1960) after coma in hypopituitarism. In their case hypotension was an important factor, though marked hypoglycaemia was present, and complete recovery of the psychosis occurred, as here. The excellent outcome in both cases after a prolonged organic psychosis is noteworthy.

Summary

A woman of 38 with Addison's disease developed hypoglycaemic coma, from which she recovered

after treatment with glucose and corticosteroids. The coma was followed by an organic psychosis which lasted for two months. The main cause of this was thought to be fluctuating hypoglycaemia. The diagnostic and therapeutic implications are discussed. She recovered completely after intensive treatment with glucose by mouth.

This patient was under the care of Dr. Donald Hunter at the London Hospital and Dr. Felix Post at the Maudsley Hospital. We wish to thank them for permission to publish.

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OCULAR SYMPATHETIC PALSY IN PERIODIC MIGRAINOUS NEURALGIA

BY

E. A. NIEMAN* and L. J. HURWITZ

From the National Hospital, Queen Square, London

Harris (1921, 1926) described the main features of periodic migrainous neuralgia, and the subject has been well reviewed recently by Symonds (1956), by Bickerstaff (1959), and by Friedman, Carton, and Horanio (1960). We have examined the clinical features of 50 patients seen at the National Hospital in the past 10 years, of whom 24 were referred in the past 18 months. The observations in this series fully confirm the description of previous authors of the natural history of the pain, its prognosis, and the response to treatment with ergotamine tartrate.

The occurrence of ocular sympathetic paralysis in migrainous neuralgia has been mentioned by several authors (Harris, 1926; Horton, Maclean, and Craig, 1939; Horton, 1956; Bickerstaff, 1959) but neither its frequency nor its significance has been emphasized. We have been impressed by the number of patients in this series who have shown evidence of an ocular sympathetic palsy, and we believe that the association provides additional evidence of the vascular aetiology of the condition.

Material

All the patients in this study were referred initially to the National Hospital, Queen Square, by their general practitioners for diagnosis.

Of the 50 patients included in this series, 47 have been seen and examined personally by us. The details of the remaining three patients have been obtained by letter from them and their general practitioners. In addition to a general medical and neurological examination, *x*-ray examinations of the skull, paranasal sinuses, and chest were obtained in all cases, and carotid arteriograms in six patients. The majority of the patients have continued to attend the hospital for treatment until their symptoms have abated and the effects of treatment have been observed. The follow-up period ranges from six months to 10 years. All the patients are still living, except one who died from chronic bronchitis. None has developed another neurological disorder.

Clinical Features of Migrainous Neuralgia

The clinical characteristics of the syndrome have been described by many. The pain is always unilateral in an attack (or in a bout of attacks) but may affect either side in different bouts of pain. The pain is severe, and may be described as 'intense', 'agonizing', or 'excruciating', it is continuous and more often steady than throbbing. It may be maximal at onset but more commonly increases in intensity, reaching a maximum in 15 to 30 minutes. Individual attacks last one to two hours and seldom longer than three hours; Symonds (1956) stated that the attacks of only three of 17 patients lasted longer than two hours, a low figure compared with the present series, in which 15 patients had pain of over two hours' duration. Of these, nine patients mentioned pain of two to three hours' duration, but the remainder (six) described longer periods, of two to six hours' duration, one of whom rarely suffered pain lasting all day.

The duration of the pain is often remarkably constant and may occur in a particular patient at a particular time of day or night with clockwork regularity, and frequently waking him from sleep in the early hours of the morning. This latter feature is reported so commonly as to be almost typical. Attacks of stereotyped pain occur daily for as many as five to six times a day for weeks or months and then a spontaneous remission of weeks, months, or years may be succeeded by a further bout of attacks. This periodicity led to the use of the term 'cluster headaches'.

The situation of maximal pain is usually in or above the eye (Table I).

The pain may radiate to the forehead, temple, cheek, and ear, rarely to the jaws or to the neck but never to the other side of the head or face. Pain did not radiate in 11 patients in this series.

*Present address: Neurological Department, St. Mary's Hospital, London, W.2.

TABLE I
SITE OF MAXIMAL PAIN IN 50 PATIENTS

Eye	Supraorbital	Cheek	Temple	Vertex	Nose
21	15	3	7	2	2

Associated features which accompanied the pain in most patients included lachrymation, suffusion of the (often ipsilateral) eye, rhinorrhoea and nasal congestion (usually unilateral), and less commonly periorbital oedema and facial flushing.

Six patients mentioned that the ipsilateral superficial temporal artery was prominent, dilated and sometimes tender during an attack.

Provoking factors were regarded as important by a few patients. A warm atmosphere was mentioned by eight patients, the (often dramatic) effect of alcohol by seven patients, worry, overwork, or stress by seven patients, and there was a single mention each of sneezing, hot flushes, bright light, stooping, and 'after a holiday'. It was rare to elicit methods of producing relief: local pressure on the neck (four), local heat (two), local cold (two), and trilene inhalation (one).

In this series the age of onset varied from 13 to 69 years with a peak incidence between 26 and 35 years. The sex incidence of 35 males and 15 females shows a higher incidence of females than in other series. The number of patients with a family history of migraine is similar to other series. There was a family history of migrainous neuralgia in three patients (Table II).

Treatment and Prevention of Attacks

The value of ergotamine tartrate either orally or parenterally has been emphasized by Symonds (1956). He found that when the patient was awakened regularly in the early morning by pain, a nocturnal injection of ergotamine might ensure a night's sleep by preventing pain.

Although a control study has not been attempted here we have found that prophylactic administration of ergotamine (usually given as Caffergot, 1 mg., in suppository form) has been convenient and effective, whereas sedatives and analgesics have been of little value. Symonds (1956) discusses the long-term regular use of ergotamine preparations and points out the potential complications of this drug, especially in elderly people. It must be emphasized that whilst prophylactic ergotamine often prevented pain entirely it would not terminate a bout of attacks; if the drug was stopped the attacks often returned. It may be necessary to continue prophylactic treatment until a natural remission occurs.

Oculosympathetic Paralysis

Signs of an oculosympathetic paralysis (either ptosis, miosis, or both) have been noted in 11 patients. In 10 of these the changes were permanent and in the other case ptosis and miosis were observed by us only during an attack of pain. The clinical features of these patients are noted in Table III. In four patients in whom attacks of migrainous neuralgia were observed personally by us, the ocular signs were seen to become more marked. Eye drops, 5% cocaine, were instilled topically in six patients with miosis. In five the miotic pupil remained smaller by 2 mm. or more than the pupil of the other eye and in the other patient by less than 1 mm. In all six, 10% neosynephrine produced rapid and full dilatation of the pupil. These results are in accordance with a sympathetic paresis as the cause of the miosis. In the four patients seen during an attack sweating was not diminished on the ipsilateral side of the face nor was this phenomenon noted or reported in any other case. However, in one patient in whom miosis was observed during an attack of pain there was accompanying ptosis. This further suggests sympathetic paresis and not parasympathetic overactivity as the basis of the small pupil. An absent corneal reflex was found on the same side as the miosis in one patient, a woman now aged 51, having severe attacks of pain in the right eye for seven years, in whom the absent corneal reflex was first noted four years ago. A right carotid arteriogram was normal. This patient is an example of what has been termed Raeder's syndrome which will be discussed in more detail later. Except in this patient other neurological signs have always been lacking. Carotid arteriography was normal in six patients.

It is notable that in those patients with oculosympathetic involvement the average age of onset of pain is 42 compared with 35 for the whole series.

TABLE II
AGE OF ONSET AND SEX

	Symonds (1956)	Bickerstaff (1959)	Friedman *et al.* (1960)	Nieman and Hurwitz (Present Series)
Total cases	17	30	83	50
Sex	82% male	70% male	Predominantly male	57% male
Age of onset	14-43 Average 26·9	Peak 30-40	30-50	13-69 Peak 26-35
Family history of migraine	35%	Many	20%	22%

TABLE III

CLINICAL FEATURES OF PATIENTS WITH OCULOSYMPATHETIC PARALYSIS

Case No.	Ocular Signs	Sex	Age of Onset	Age when Ocular Signs Noted	Maximum Site of Pain	Associated Signs during Periodic Pain	Periodicity of Pain	Carotid Arteriogram
1	Ptosis + miosis	M	32	34	R. eyeball	Lachrymation, periorbital oedema	Daily attacks in bout, three bouts in seven years	
2	Ptosis + miosis	M	69	71	R. frontal	—	First bout daily for four months, second bout daily for six months	
3	Ptosis + miosis	M	56	60	R. eyeball	Lachrymation, conjunctival suffusion periorbital oedema	Two bouts a year for nine years, daily attacks	Normal
4	Ptosis + miosis	M	31	45	L. supraorbital	Lachrymation	Bouts every two years for 14 years, three attacks a day for three weeks	
5	Ptosis + miosis (bilateral)	M	33	R.48 L.55	Temple	Ipsilateral rhinorrhoea	Four bouts in 22 years (3 R. and 1 L.), three to four attacks daily for three months	Normal
6	Ptosis + miosis	M	42	42	R. cheek	Lachrymation, conjunctival suffusion, ipsilateral rhinorrhoea	Bouts every two years for 12 years, daily attacks recently for one and a half years	
7	Miosis	F	44	47	R. eyeball	Absent corneal, lachrymation, conjunctival suffusion, nasal obstruction, ipsilateral rhinorrhoea	Daily attacks for two weeks, (longest remission: two months in seven years)	Normal
8	Miosis	M	54	60	R. eyeball	Lachrymation, conjunctival suffusion, periorbital oedema, ipsilateral rhinorrhoea	Bouts every two years for nine years, daily attacks for four months	
9	Ptosis	F	44	51	R. inner canthus	Lachrymation, conjunctival suffusion, ipsilateral rhinorrhoea	Two to three bouts a year for seven years, daily attacks for three months	
10	Ptosis	M	35	48	R. eyeball	Lachrymation, ipsilateral rhinorrhoea	Daily attacks for six months, one bout a year for 13 years	Normal
11	Ptosis	F	40	51	R. eyeball	Periorbital oedema	Duration 11 years, attacks every day for a month, remissions of two months	Normal

The average age of onset of oculosympathetic paralysis in the 13 patients is 49. In four patients the interval between the onset of migrainous neuralgia and the development of ptosis and/or miosis was over 10 years.

Of particular interest is Mr. H. G., aged 55. His symptoms began in 1938 at the age of 33. He complained of lancinating pain in the right eye, radiating to the cheek and temple and waking him from sleep at 2 a.m. every morning for three months. There was then a complete remission until 1944 when he had a similar bout affecting the right eye and a further right-sided bout in 1953. His fourth and last bout, however, in 1960 was left-sided, maximal over the temple and radiating to the eye and cheek. Antrum washouts were performed in 1938, a submucous resection of the nose in 1944. A right carotid arteriogram in 1953 was normal. In 1953 he noticed that during each attack the right eyelid drooped markedly and the right pupil became pin-point. Since that time he has had a permanent right-sided ptosis though the right pupil is now of normal size. In the recent bout of pain in 1960, however, he noticed left-sided ptosis and miosis and the left pupil was found on examination (during an interval between attacks of pain) to be smaller than the right.

He produced at one interview the following summary of his personal observations during attacks from April 28, 1960, to June 7, 1960.

1 Mental activity or complete relaxation appear to precipitate an attack.

2 Some tension or tightness in the left temple approximately 10 to 15 minutes before severe pain occurs.

3 Very high frequency whistle in head when attack pending.

4 Sharp, stabbing pains in left temple spreading to scalp, eye, and cheek.

5 'Veins' in left temple distend and feel hard to touch.

6 Obstruction occurs in left nostril.

7 Left pupil contracts, left eyelid droops. Eyes bloodshot.

8 Scalding or searing sensation in left nostril in some instances.

9 Perspiration on left of head during an attack.

10 Slight flow of clear mucus from left nostril as pain passes.

11 Tender or sore feeling in scalp after attack.

12 Attack usually followed by indigestion.

The incidence of 22% of patients with an oculosympathetic paresis is unexpectedly high. This may in part be due to the fact that 'simple' cases of migrainous neuralgia, *i.e.*, without signs, and responding well to treatment may not have been included in the hospital diagnostic index.

Discussion

Many names have been given to this type of cyclical facial pain: periodic migrainous neuralgia, Harris's neuralgia, cluster headaches, erthromelalgia of the head, histamine cephalalgia, red migraine, ciliary neuralgia, and others. It probably also embraces a number of other ill-defined (but supposedly distinct) syndromes such as Vidian neuralgia, Charlin's syndrome, and some cases of paratrigeminal neuritis (Raeder's syndrome). It was given its first clear description by Harris (1926) and has been more recently described and discussed by Symonds (1956), by Bickerstaff (1959), and by Friedman *et al.* (1960).

It is generally accepted that whatever the basic cause of the disturbance may be, the mechanism of the pain is stimulation of pain-sensitive fibres by vascular dilatation. Analysis of the site and radiation of the pain in all our cases suggests that the dilatation takes place in the territory of the internal and external carotid arteries. The more readily observable manifestations of this vascular dilatation are obvious in the flushing, increased warmth, and pulsating superficial temporal vessels. This superficial component, which implicates the external carotid artery, may be contrasted with the deep, boring, ocular pain which suggests an internal carotid artery origin. It is well recognized that some patients obtain relief by digital compression of either the superficial temporal artery or of the common carotid artery in the neck. That vasodilatation is responsible for the pain is supported by Horton's (1952) demonstration that the pain can be reproduced by injection of histamine. He was also able to abolish the histamine-induced pain with a vasoconstrictor (epinephrine). The efficacy of ergotamine tartrate in aborting a clinical or induced attack is due to its vasoconstrictor action which may also be employed prophylactically.

A phenomenon which has been noted by a few writers, but which has not been emphasized and its significance neglected, is the occurrence (either as a transient or as a permanent accompaniment) of an ocular sympathetic paralysis. Harris (1926) describes the case of a man aged 47 who noticed miosis and ptosis in his first attacks. This was present when Harris examined him and remained permanent. He discusses the mechanism and causation of this involvement. He says that the site does not seem to be in the ciliary ganglion because one would have expected parasympathetic effects and ocular muscle involvement, which were not present.

Horton mentions in his papers in 1939 and 1956 that a Horner's syndrome is not uncommon in 'histamine cephalgia'. He does not give the number of cases in which this was observed. Friedman and Merritt (1959) state that 'a few patients with various forms of migraine present during the headache other signs of central neural activity, such as miosis and nasal congestion soon after the headache. These features suggest an integrated parasympathetic discharge of which the vasodilator headache is only one, although the most prominent feature'. Our observations, however, indicate a sympathetic paralysis, rather than a parasympathetic stimulation.

More recently Kunkle and Anderson (1960) have reported their findings of transient and persistent oculosympathetic signs in this condition. Of their 90 patients, six showed as a transient phenomenon miosis alone, and one showed miosis and ptosis. Seven patients showed persisting signs (two with miosis alone and five with ptosis in addition). They postulate that the fault results in some way from repeated dilatations of the internal carotid artery, and the sympathetic involvement occurs close to the carotid siphon.

In this series ocular sympathetic involvement occurred in 22% of cases.

Our findings emphasize the benign nature of the associated ocular sympathetic palsy when it occurs. It may disappear or lessen between attacks. Ocular sympathetic changes are found usually in patients who are middle-aged (youngest 34 but majority over 45) and have had repeated bouts of attacks.

The combination of periodic facial pain and a Horner's syndrome was also described in a group of cases by Raeder (1924). He described five patients; in one it was due to neoplasm in the middle cranial fossa, in two to local trauma, and in two cases no cause was discovered. In four of these the trigeminal nerve was involved with appropriate anaesthesia and he designated the picture the paratrigeminal syndrome. His Case 4, where no cause was found, was the only patient without involvement of the trigeminal nerve. He felt that the lesion in these cases must be at the base of the middle fossa damaging the ocular sympathetic fibres in the wall of the internal carotid artery.

Ford and Walsh (1958), in a paper entitled 'Raeder's Paratrigeminal Syndrome', are in agreement with Raeder that in these cases the lesion must be at the base of the middle fossa on the basis of their observations of a series of 25 cases in which 'only pain above the eye and the oculosympathetic phenomena' were present. We think the term Raeder's syndrome should be reserved for cases in which there is clear evidence of a local lesion causing signs of trigeminal nerve involvement in conjunction with ocular sympathetic palsy and pain in the trigeminal distribution. Raeder's syndrome (thus defined) can be due to a number of local causes, including trauma and neoplasm.

It has been suggested by Wolff (1948) that in a migrainous attack the artery becomes dilated, and that when the dilatation is prolonged, oedematous thickening occurs in its wall. The ocular sympathetic nerve fibres lie in the sheath of the internal carotid artery and might therefore be compressed.

Ocular sympathetic palsy has also been described in internal carotid artery occlusion where there is no evidence of a brain-stem disturbance (O'Doherty and Green, 1958). The most likely explanation is oedema or ischaemia of the carotid artery as a result of the thrombotic occlusion. It seems reasonable to conclude that dilatation of the carotid artery may produce pain and transient involvement of the sympathetic pathways, as in our cases of migrainous neuralgia; repeated dilatation may occasionally produce a permanent sympathetic lesion.

In referring to ocular sympathetic paralysis we have been careful not to use the term Horner's syndrome, as this term implies in addition to ptosis and miosis, unilateral anhidrosis. Although the latter was looked for, it was never encountered in this series, nor have other authors mentioned it. The sudomotor fibres travel along the external carotid artery, but although dilatation of the external carotid artery accounts for many of the manifestations of migrainous neuralgia, the involvement of the ocular sympathetic pathways is likely to be in the intraosseous portion of the internal carotid artery because there they would be particularly liable to damage against the bony wall.

Periodic migrainous neuralgia is therefore a relatively benign condition and recognition of the clinical features will save the patients unnecessary investigations and operations. The finding that the fifth cranial nerve is involved, however, makes it probable that there is some structural lesion in the middle cranial fossa.

Summary

The clinical features of 50 cases of periodic migrainous neuralgia have been studied.

Ocular sympathetic paralysis or paresis was present in 11 patients (22%) and the mechanism has been discussed.

The relation of periodic migrainous neuralgia to Raeder's syndrome has been discussed and it is suggested that the latter term should be reserved for cases in which there are signs of trigeminal nerve involvement in addition to ocular sympathetic palsy and pain in the trigeminal distribution.

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RADIOLOGICAL AND CLINICAL FEATURES OF AN ARACHNOID CYST OF THE QUADRIGEMINAL CISTERN

BY

HERBERT LOURIE and ALFRED S. BERNE

From the Division of Neurological Surgery and the Department of Radiology, State University of New York, Upstate Medical Center, and the Sycracuse Memorial Hospital, Syracuse, New York

Cummins, Taveras, and Schlesinger (1960) have emphasized again the high mortality rate associated with surgical exploration of lesions in the region of the posterior third ventricle. However, there are certain benign processes which occur in this area which require definitive surgical treatment rather than shunting procedures and/or radiation therapy, and the successful management of obstructing mass lesions in this critical area is dependent upon correct pre-operative diagnosis.

This report records an example of an arachnoid cyst of the quadrigeminal cistern. Nine similar cases have been recorded previously. Hamby and Gardner (1935) described a 16-year-old girl who complained of deafness and suffered from increased intracranial pressure resulting from an ependymal cyst in the supracollicular area. Their patient recovered after surgical evacuation of the cyst through the anterior medullary velum. Although the cyst wall was composed of ependymal cells there was neither radiological nor surgical evidence of a communication between the cyst and the ventricular system. Alexander (1953) reported an 18-month-old patient with an arachnoid cyst of the quadrigeminal cistern. Severe obstructive hydrocephalus was relieved by the operative establishment of a communication between the posterior end of the third ventricle and the cyst. This child, when evaluated three years post-operatively, showed residual spasticity and moderate retardation on psychological testing. Dott and Gillingham (1958) described an infant suffering from spasticity and an enlarging head. A large arachnoid cyst of the supracollicular region was drained through the right ventricle, but the patient died of a post-operative haematoma. Katagiri (1960) recorded two cases of arachnoid cyst of the cisterna ambiens, but the illustrations indicated that these lesions were in fact in the quadrigeminal cistern. Both patients were adults. One died after surgery; the other was 'cured' by ventricular taps. Noetzel (1940) reported three patients with cysts in the cisterna ambiens in whom the symptoms resembled the clinical picture of pineal tumour. Hoshino, quoted by Katagiri (1960), recorded one case in which a cyst in this area produced ventriculographic findings suggestive of a tumour of the quadrigeminal plate. Dyke (1959), in 'Diagnostic Roentgenology', illustrated a lateral film from a ventriculogram which was labelled a 'cyst of dura'. His case, in our opinion, would seem to represent an arachnoid or ependymal cyst of the quadrigeminal cistern.

Case Report

A 13-month-old boy was admitted to the Syracuse Memorial Hospital on March 29, 1960, because of regression in neuromuscular function and a rapidly enlarging head. The baby had developed normally to the age of 10 months at which time he could stand with help and spoke a few simple words. He then became irritable, slowly lost the ability to stand or sit, and at 12 months developed an internal squint of the right eye.

The mother's pregnancy and delivery were uneventful. There was no history of infectious disease in childhood.

Physical examination revealed a very irritable child. The skull was enlarged (52·5 cm. maximum circumference), but the scalp veins were flat and no cranial bruit was heard. Neurological examination demonstrated a right abducens palsy, bilateral papilloedema, a positive MacEwen's sign, and severe generalized spasticity and clonus. The blood count and urine analysis were indeterminate. Plain skull films showed widened sutures, an enlarged vault, and a simple linear fracture in the right parietal bone.

On the second hospital day subdural taps were performed through the enlarged anterior fontanelle, but no fluid was obtained.

Two days later contrast radiographs were obtained. (A detailed description of the pertinent films made during this and subsequent studies is given beneath Figs. 1 and 2.)

A gas ventriculogram was performed first because of

FIG. 1A

FIG. 1B

FIG. 1.—Lateral (A) and frontal (B) films of the skull made with the patient in the brow-up position following air ventriculography, attempted pneumoencephalography, and Pantopaque ventriculography.

The gas outlines the undisplaced anterior portion of a markedly dilated third ventricle (↕) and symmetrically dilated frontal horns. The Pantopaque outlines the posterior inferior portions of the dilated third ventricle and the aqueduct of Sylvius (A). The suprapineal recess is bowed and displaced upward and forward, and the junction of the third ventricle and aqueduct and the proximal aqueduct are bowed forward anteriorly and inferiorly in a smooth curve. (A↑) The distance from the aqueduct to the dorsum sellae is markedly reduced. The aqueduct is not visualized in (B) because it is obscured by the opaque oil in the posterior inferior third ventricle.

FIG. 2A

FIG. 2B

FIG. 2.—Frontal (A) and lateral (B) skull films made with the patient erect and with the neck semiflexed during the post-operative pneumoencephalogram after the first craniotomy.

At this time the aqueduct was not obstructed and gas passed into the third ventricle and right lateral ventricle from below. The fourth ventricle is seen (↑) widened from side to side and diminished in its cephalo-caudad dimension. There is no lateral displacement of the fourth ventricle but it is displaced caudad.

The roof of the dilated third ventricle and the displaced and dilated suprapineal recess are outlined with gas. (↕) The two air-fluid levels visible are probably due to the indentation of the posterior portion of the roof of the third ventricle by kinking forward of the corpus callosum.

the presence of brain-stem signs and increased intracranial pressure. The posterior fossa structures were not well visualized. Therefore, a lumbar pneumoencephalogram was attempted. Finally, in order to define the aqueduct 1·5 ml. of Pantopaque was introduced into the right lateral ventricle.

On March 4, 1960, a craniotomy was performed to permit infra- and supratentorial exploration. The cerebellar tonsils were herniated through the foramen magnum, more marked on the left. Both cerebellar hemispheres were bulging, more so on the left. There was no evidence of arachnoiditis and the fourth ventricle was not obstructed. A large thin-walled cyst, containing clear fluid, was found between the anterior surface of the cerebellum and the tentorium. The cyst had stretched the tentorial incisura markedly and the major portion of the cyst lay supratentorially. The cyst contents were aspirated and the infratentorial dome of the cyst was removed, thereby establishing communication posteriorly with the superior cerebellar cistern. Indigo-carmine injected at this time into the lateral ventricles quickly appeared in the fourth ventricle, but did not enter the cyst. Microscopic examination of the wall of the cyst revealed a 'benign cyst composed of mesodermal structures of arachnoidal origin'. No inflammatory cells were seen in the cyst wall and there was no pigmentation to suggest that the cyst had resulted from haemorrhage (Fig. 3).

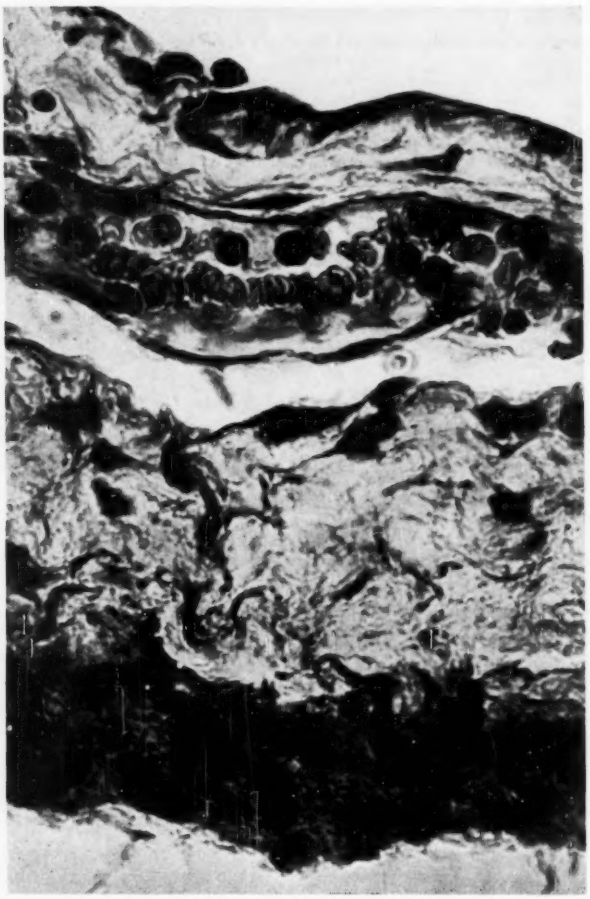

FIG. 3.—Photomicrograph of cyst wall. The inner surface is at left. The wall consists of loose connective tissue cells with an occasional capillary. Haematoxylin and eosin × 650.

The post-operative course was complicated by a subcutaneous collection of fluid which necessitated a second surgical procedure to close a pinpoint dural fistula overlying the cisterna magna. Thereafter the patient did well and was discharged with much less spasticity. Improvement continued for the next six months. On November 30, 1960, the patient was re-admitted to the hospital because of vomiting of two weeks' duration. Physical examination revealed an irritable child with a soft bulge in the suboccipital area. The head circumference was now 54·5 cm. and the papilloedema and spasticity had recurred. It was thought safe to perform a lumbar penumoencephalogram because of the previous suboccipital decompression. The encephalographic findings were identical with those demonstrated originally.

On December 2, 1960, the cyst was approached through an occipital osteoplastic flap. At this operation a medical artist was present and his concept of the lesion is illustrated in Fig. 4. On this occasion a 1 cm. communication was established between the posterior end of the third ventricle and the anterior wall of the cyst. A second and larger communication was made by removing a portion of the medial wall of the left occipital horn and fixing the ependyma of the horn to the cyst wall with two silver clips. Fluid aspirated from the cyst contained 93 mg. % protein compared with 4 mg.% in the ventricular fluid and 8·5 mg.% in the lumbar spinal fluid. The post-operative course was uneventful. All signs of increased intracranial pressure subsided. Since the time of writing, the child has been seen for his 16 months' follow-up examinations. He continues to show motor and intellectual improvement.

Radiological Features

Cysts of the quadrigeminal cistern can be classified radiologically as posterior incisural lesions as described by Taveras (1960). This lesion produces obstructive hydrocephalus by stretching the aqueduct forward and inferiorly, compromising its lumen. The posterior margin of the third ventricle is encroached upon and is displaced forward in a very smooth, rounded fashion. The suprapineal recess is elevated and bowed around the cyst. When the cyst extends infratentorially it will depress, flatten and widen the fourth ventricle. Obviously the quadrigeminal cistern cannot be filled with gas. The pontine and crural cisterns may be smaller than usual due to brain-stem displacement but they are not obliterated. In our case the posterior portion of the roof of the third ventricle was indented by a soft tissue mass, probably caused by forward buckling of the splenium of the corpus callosum.

The important point in diagnosis would appear

FIG. 4.—Artist's concept of the operative findings.
Note the marked forward displacement of the third ventricle, and the downward displacement of the anterior cerebellum. The lesser veins of Galen are separated and they and the great vein are displaced downward by the floor of the cyst.

III V = third ventricle
SCC = splenium of corpus callosum
SPR = suprapineal recess
SSS = superior sagittal sinus
ISS = inferior sagittal sinus
Tent = tentorium
VG = vein of Galen
SR = sinus rectus
TS = transverse sinus

to rest upon recognition of the marked stretching and bowing of the structures in the vicinity of the posterior tentorial notch, suggesting the presence of a relatively soft mass such as a cyst, and permitting the development of marked internal hydrocephalus. Lateral displacement of the midline structures, *i.e.*, the third ventricle, aqueduct, and fourth ventricle, is not present because the cyst originates from the centrally situated quadrigeminal cistern.

Absolute radiological diagnosis would be possible only if contrast material entered the cyst, but this is unlikely unless the cyst were tapped intentionally or inadvertently during gas ventriculography. However, this gas-filled cavity should not be confused with the enlarged but not displaced suprapineal recess occasionally seen in association with hydrocephalus, *i.e.*, 'suprapineal diverticulum'.

Angiography was not performed in this instance. However, observations made at surgery indicated a forward bowing and separation of the lesser veins of Galen as they passed around the cyst before joining to form the great vein of Galen (Fig. 4).

Radiological Differential Diagnosis

The first step in differential diagnosis should be the elimination of lesions other than incisural masses which cause symmetrical dilatation of the lateral and third ventricles.

Infratentorial lesions such as supra- or infrafastigial cerebellar masses can be excluded because they kink the aqueduct forward with the apex of the kink at the intercollicular level. Upward herniations through the tentorium may mask these classical findings (Twining, 1939).

Masses anterior to the aqueduct are easily differentiated because they bow the aqueduct posteriorly and/or laterally and may rotate the brain-stem, aqueduct, and fourth ventricle. Complete obstruction of the aqueduct is rare with these anterior lesions, and when the third ventricle is impinged upon it is usually the floor of the third ventricle rather than the posterior portion which is distorted. If the basal cisterns are delineated with gas they are partially obliterated.

Stenosis of the aqueduct characteristically occurs at its most rostral portion and causes no local deformity of the third ventricle.

The four lesions which are most likely to be confused with a cyst of the quadrigeminal cistern are pinealoma, aneurysmal dilatation of the vein of Galen, midline meningiomas arising from the posterior tentorial notch, and central gliomas invading the quadrigeminal plate. Pinealomas encroach most severely upon the posterior end of the third ventricle. The pineal recess is obliterated and the suprapineal recess is displaced upward or obliterated, depending upon the size of the pineal tumour. However, since pinealomas are usually solid tumours, total occlusion of the aqueduct tends to occur early and therefore marked elongation and bowing of this structure would be less likely to occur. Infratentorial extension of pinealomas is rare. At angiography the distal portion of the internal cerebral veins and the vein of Galen should be raised and bowed upward and backward. However, none of these differential points is absolute.

Aneurysm of the vein of Galen may produce all of the radiological signs of the lesion under discussion here when studied by encephalography, but angiography should make the differentiation. In retrospect such a procedure might well have been performed in our patient, although the clinical picture was not suggestive of a vascular lesion (Russell and Nevin, 1940). Posterior incisural meningiomas may produce similar encephalographic findings although the manifestations of a relatively soft mass will be less likely to occur (Taveras, 1960). The displacement of the deep veins at angiography is very similar to that visualized at surgery in our case.

Gliomas invading the quadrigeminal plate will straighten the aqueduct and displace it forward but are unlikely to bow and stretch it as happened with this cystic lesion (Lysholm, 1946). Lateral displacement of the aqueduct would be likely because the gliomas are usually not strictly midline lesions.

Discussion

The aetiology and mechanisms of cyst formation in the subarachnoid pathways are not clearly understood. It is likely that they result from more than one cause. Hamby and Gardner (1935) thought in their case that the cyst had formed from a ventricular diverticulum, but since their patient had suffered a fall they could not exclude trauma as a causative factor. Alexander's (1953) patient had had severe pertussis at the age of 5 months so the cyst could not necessarily be considered congenital in origin. In Dott and Gillingham's (1958) case there was a history of 'minor birth trauma' so that again trauma could not be excluded as the basic mechanism for the cyst formation.

Our patient had sustained a linear skull fracture but whether the trauma which produced the fracture was the cause of the cyst or the result of the child's ataxia secondary to the presence of the cyst, cannot be ascertained. The absence of pigment or inflammatory changes in the cyst wall seem to make trauma unlikely as the precipitating factor.

Dott and Gillingham (1958) postulated that some inflammatory factor such as blood or exudate might initiate a pathological process which could obstruct the outlet of any of the subarachnoid cisterns. Cerebrospinal fluid would then continue to enter the partially blocked cistern as it was 'milked' or pumped forward by transmitted pressure waves from nearby pulsating arteries. This mechanism would then gradually result in distention and increased pressure in the obstructed cistern.

From the evidence it is impossible to state whether the cyst in our case represented an aquired or a congenital lesion, although we consider the latter the more likely possibility.

Summary

An example of obstructive hydrocephalus secondary to a large cyst of the quadrigeminal cistern is reported.

The salient radiological features and the differential diagnosis of this lesion are discussed.

The importance of suspecting and directly treating these benign masses is stressed.

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J. Neurol. Neurosurg. Psychiat., 1961, **24**, 379.

SUPRACHIASMAL MENINGIOMA IN A 2-YEAR-OLD CHILD

BY

PAUL TENG

From the Neurosurgical Service, Kaiser Foundation Hospital, Los Angeles, U.S.A.

Intracranial meningioma is a rare tumour in children. In Cushing and Eisenhardt's book (1938) on meningiomas, six occurred in the pre-adolescent age group. A review of the literature found six patients to be under 2 years of age with only one survival (Stern, 1937; Bailey, Buchanan, and Bucy, 1939; Grant, 1947; Cuneo and Rand, 1952). The present report concerns a case of giant meningioma successfully removed from a 2-year-old boy. The tumour was unusual in location, suprachiasmal, and unusual in size, 250 g.

Case Report

A 2-year-old boy was admitted to the hospital on January 14, 1960, his second birthday. He had apparently been well until about nine weeks ago when he vomited repeatedly and gradually became listless, apathetic, irritable, and cross-eyed. The mother stated that he was frequently noted with his right eye turned inward since he was 2 months old. About one month before admission both his hands were shaking, the right more than the left.

Neurological examination showed that the child was not lethargic but listless. He weighed 26 pounds. The head appeared larger than normal, and measured 56 cm. in circumference. Markedly dilated veins were noted in both frontal areas. There was a positive Macewen's sign on percussion. Both pupils were normal in size and reacted well to light. Gross visual field examination showed no defect. There was a mild weakness in the left lateral rectus muscle. Choked disc was noted on both sides. The right arm was hypotonic and weak. Fine tremors were noted in the hands, especially the right. Deep tendon reflexes were all brisk and equal on both sides. No pathological reflex was elicited. A radiograph of the skull showed marked separation of cranial sutures, especially the coronal, at places about 2 cm. wide.

A lumbar puncture showed a pressure of 219 mm. water, and the total protein content was 300·07 mg. %.

On January 18, 1960, under general anaesthesia a ventriculogram was performed through the separated coronal suture. On the right side, at a depth of about 2 cm. from the skin, the ventricular needle was deflected to the side by a hard mass. Five ml. of air was injected along the surface of the mass (Fig. 1). A similar attempt for a ventricular tap on the opposite side was made and the needle again failed to enter the ventricle but the same resistance was encountered. Another 5 ml. of air was instilled in this side. The injected air outlined a huge lobulated mass in the anterior and middle fossa extending from the midline to both sides.

After the ventriculogram, the patient was operated upon. Two vertical incisions, 2½ in. long, were made in the frontal vertex across the coronal suture and a craniectomy window, 2 × 2 in. in size, was made on each side. The dura flaps were reflected toward the midline, and were sutured temporarily over the scalp. The frontal cortex was noted to be atrophic with obliterated sulci and gyri. Both frontal lobes were pushed backward by an enormous tumour with a hard, nodular, pinkish white glistening surface. The tumour was well encapsulated. It extended anteriorly to the frontal pole of the cranial cavity, posteriorly about 5 cm. behind the coronal suture, and laterally about 3 cm. from the temporal bone on both sides. It was removed piecemeal by intracapsular excavation. The collapsed capsule was lifted easily off the floor of the middle fossa. The optic nerves, chiasm, and optic tracts were markedly stretched downward and posteriorly by the tumour. The flattened optic nerves, chiasm, and optic tracts resembled a small concave hammock upon which had nested a giant meningioma which weighed 250 g. Both internal carotid arteries were depressed and pushed laterally by the tumour. No dural attachment of this tumour was noted. Its blood supply was mainly from the ethmoid arteries.

FIG. 1.—Perineoplasm injection of air outlines the lobulated lateral surface of the tumour.

FIG. 2.—Patient photographed one year after surgery.

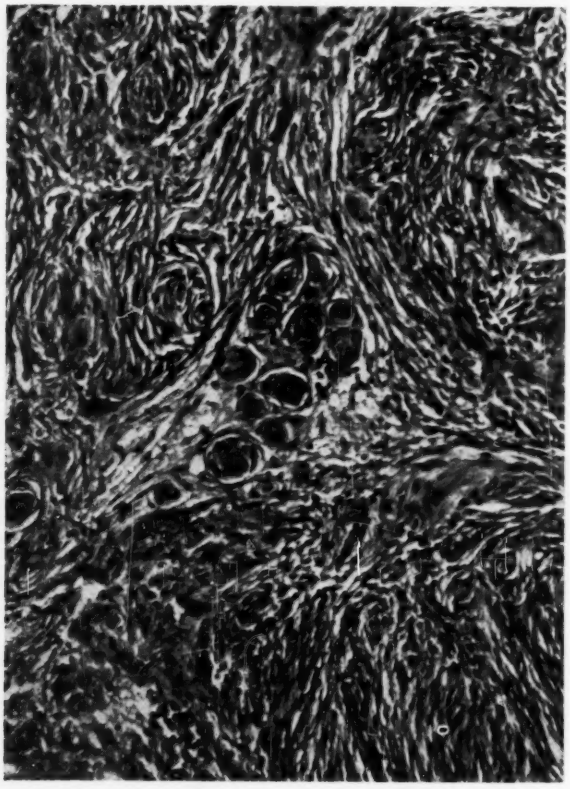

FIG. 3.—Meningioma. × 100.

The post-operative course was uneventful, and the child has made a complete recovery (Fig. 2). The sixth nerve palsy had largely disappeared three months later. His speech was clear and he recited nursery rhymes well. He was active, often 'overactive', and had frequent tantrums.

The pathological diagnosis was psamomatous meningioma (Fig. 3).

Comment

A review of the literature revealed several unusual features of intracranial meningioma in children. They are (1) often large or enormous with (2) minimal neurological signs as a result of compensatory head enlargement through separated sutures, (3) more frequent recurrence of growth, (4) higher incidence of sarcomatous change than in adults, (5) lack of dural attachment, and (6) high operative mortality.

In the present case the ventriculogram was performed through the widely separated coronal suture instead of through a regular burr hole, and air was injected between the tumour and the neighbouring surface of the brain instead of intraventricularly. The enormous tumour had displaced the ventricular system posteriorly and shielded it from in front, and therefore, any attempt to reach the lateral ventricle by a frontal puncture would be impossible. The perineoplasm deposition of air had clearly outlined the tumour. The neoplasm was removed through two small craniectomy rectangular windows made through the widened coronal suture lateral to each side of the sagittal line. The exposure of the tumour was satisfactorily adequate throughout the operation. After the intracapsular excavation of the tumour, the capsule was easily lifted off a remarkably stretched optic chiasm. In spite of the fact that the optic tracts, chiasm, and optic nerves were flattened ribbon-like, it is gratifying to note that there has been no visual disturbance. Both fundi showed no evidence of atrophy.

Summary

A case of a large intracranial meningioma in a 2-year-old child has been described. The tumour was successively removed from the anterior and middle fossae. Here it had rested directly upon the optic nerves, chiasm, and tracts.

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EXTRADURAL HAEMATOMA AT THE VERTEX*

BY

G. L. ALEXANDER

From the Department of Neurological Surgery, Frenchay Hospital, Bristol

The wider use of angiography in the investigation of cases of head injury in Bristol has revealed several cases of extradural haematoma at the vertex associated with raised intracranial pressure. It is submitted that a median extradural effusion at or near the vertex compresses the sagittal sinus, and, probably more importantly, the venous lacunae, resulting in a degree of engorgement of the hemispheres.

Case Reports

Case 1.—A man, aged 36 years, was found unconscious an uncertain time after a motor-cycle skid. He recovered during the next hour sufficiently to be able to give some response to questions. The left pupil did not react to light. All limbs moved well. Later the right pupil dilated and also failed to react to light. In a few hours the pulse rate dropped from 80 on admission to 66/min. Paraldehyde was given. The patient was unconscious and incontinent by 12 hours after injury, and the plantar responses became extensor in type.

When he came under neurosurgical care an hour later a flaccid left hemiplegia was evident. The limbs on the right side showed a tendency to decerebrate posturing in response to stimuli. The most striking finding was a quite exceptional engorgement of retinal veins bilaterally, with early papilloedema. There were no retinal haemorrhages in spite of the gross turgidity of the veins. The pulse was at times below 60/min. The right temporal region exhibited a haematoma under the scalp in relation to extensive fissuring of the calvarium. One fissure extended in a coronal plane across the vertex.

Angiography (Fig. 1) revealed a depression of the sagittal sinus away from the calvarium in the frontoparietal region, and some narrowing of its lumen. It is significant that to obtain this picture the radiologist (Dr. J. L. G. Thomson) had to make a further injection and an exposure fully two seconds later than customary for this phase. The anterior cerebral artery was but slightly deviated to the left of the midline in the anteroposterior view.

At operation a quadrangular plate of bone, 6 × 8 cm. in size, centred with a bias to the right side, was removed at the vertex, its posterior limit being the transverse

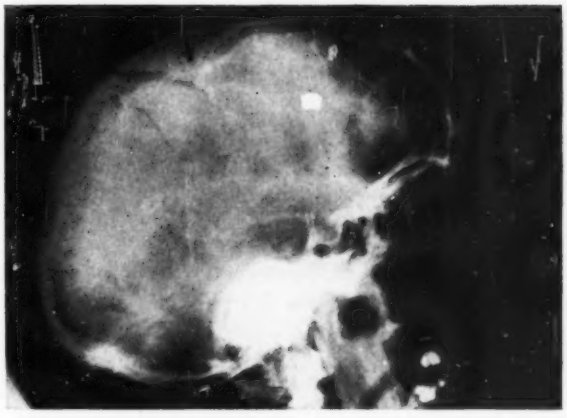

FIG. 1.—Case 1: late-exposure venogram.

fissure fracture. This exposed the whole of a localized extradural clot of 2 cm. maximal thickness. When the clot was removed the dura mater was seen to be intact and under nearly normal tension. The plate of bone was replaced.

Next morning, about 12 hours after operation, the hemiplegia had vanished completely. The retinal engorgement had subsided. The patient was able in a limited way to obey commands. Tracheostomy became necessary on the second post-operative day. For the first 12 days both pupils remained fixed and dilated, yet he was able to comprehend and soon to speak. The eyes were divergent, and the plantar responses remained extensor. On the twelfth day the left pupil began to react feebly to light, and simultaneously the plantar responses became normal. On discharge home after five weeks in hospital the right pupil was still inactive and the eye remained deviated outwards. The fundi were normal, and in all other respects the patient was very well. The third nerve palsy has since recovered.

The clot in this case was not of large volume but it was strategically situated so as to compromise venous drainage from the hemispheres superiorly, and give rise to a diffuse congestion of the hemispheres, just the conditions in which a complete or 'ring' herniation would occur at the tentorial aperture, with dorsal compression of the midbrain. The early return of consciousness and in contrast

*Based on a communication given to the Society of British Neurological Surgeons in Copenhagen on May 12, 1961.

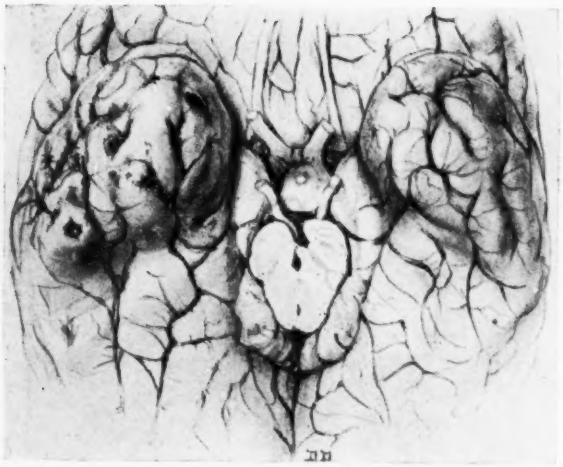

FIG. 2.—A 'ring herniation' and grooving of each third nerve by the petro-clinoid ligament. (By courtesy of Messrs. Butterworth and the author.)

the long persistence of third nerve dysfunction indicate that the midbrain escaped structural damage, and that the third nerves were compressed against the petro-clinoid ligaments. Johnson (1957) figures well the morbid anatomy envisaged in this case (Fig. 2).

Case 2 (by courtesy of Mr. D. G. Phillips).—A man, aged 23 years, who was a known diabetic fell from his horse while riding alone and was rendered unconscious. He recovered after an uncertain interval and walked some distance home. Frontal headache and vomiting persisted for five days, then he became drowsy and was admitted to hospital. The only important neurological findings were papilloedema, and rigidity of neck muscles, with a positive Kernig sign. The clear and colourless lumbar fluid was under a pressure of 300 mm., containing 264 red cells/c.mm. The blood sugar was 214 mg. per 100 ml.

Next day headache and drowsiness increased, and the left plantar response became extensor in type. The patient was transferred to neurosurgical care. No new findings were elicited. Pulse and respiration rates were on the slow side. The pupils were normal. The papilloedema and the asymmetry of plantar reflexes were confirmed. The bladder was distended. The blood sugar had risen to 502 mg. per 100 ml.

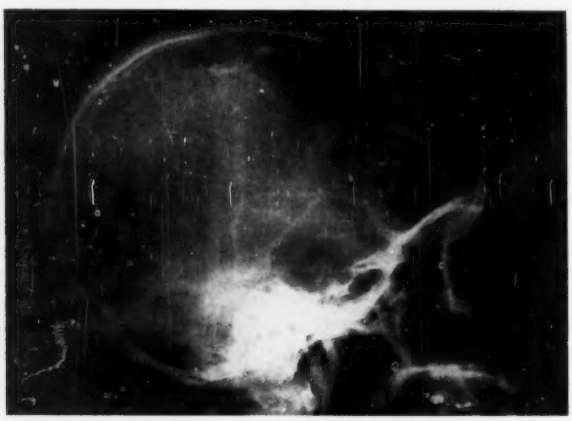

FIG. 3.—Case 2: lateral angiogram.

Angiography showed an extracerebral effusion of some size, level with the parietal region (Fig. 3), and it is to be noted that the film shows evidence of a retarded cerebral circulation. The exposure was made at the interval of time after injection which usually shows cerebral veins and the sagittal sinus in part. The anterior cerebral artery was median in position, but in the lateral view was displaced considerably downwards in the posterior part of its course. It is important that the sagittal suture had been 'sprung' by the blow on the head.

Paired parietal burr holes were made not far from the midline, and a quantity of fluid blood and some clot was evacuated from the extradural space. Bleeding apparently ceased and the wounds were closed, with drainage.

Headache and vomiting continued, and catheterization of the bladder was necessary. Two days after the intervention the burr holes were re-exposed and a further accumulation of fluid blood and clot was evacuated. When saline was injected into the lumbar theca a small additional amount of old clot was extruded. Ventriculography showed nothing alarming. Thereafter improvement began, after an initial tendency to drowsiness, and urinary retention. The blood sugar was kept well under control. At the time of the patient's discharge home a month after admission the papilloedema had not quite subsided, and the left plantar reflex was still extensor in type. When seen two months later the patient was in excellent condition, with normal fundi.

In this case the sagittal sinus and drainage of blood into it was compromised more posteriorly than in the previous case, and the important Rolandic veins probably escaped severe compression. The syndrome was certainly much more benign and slower in its development than in Case 1.

Osteoplastic craniotomy would have been more effective, but lesser measures were preferred, and were successful, in this known diabetic case.

Case 3.—A man, aged 46 years, immediately lost consciousness lasting for about 20 minutes after a motorcycle accident. Radiographs showed a fissure fracture of the vault disposed antero-posteriorly and crossing the midline. On admission to hospital a fairly large haematoma was evident under the scalp at the vertex. The pulse was 88/min. No abnormal neurological findings were apparent. Headache and vomiting continued after admission, and on the fourth day the pulse rate had fallen to 56/min. Headache increased and next day early papilloedema was seen. No new abnormal neurological signs were found on transfer to the neurosurgical unit: in particular, the plantar responses were normal. Carotid angiography showed separation of the sagittal sinus away from the vault of the skull over a considerable extent (Fig. 4). The pulse quickly returned to a normal

FIG. 4.—Case 3: lateral angiogram.

rate and headache ceased over the next two days. On that account operation was deferred. On the ninth day after injury lumbar puncture revealed a pressure of 270 mm.; the colourless fluid was normal. When the patient was transferred to the hospital of origin after 10 days of observation the ocular fundi were normal and he had remained free from symptoms.

In this case the clot was thin and perhaps extensive, so that there was no focal compression of the sinus and its tributaries.

The last case in this series is of interest because the extradural haemorrhage was larger than in any of the foregoing cases. It was located more anteriorly. The angiogram seems to show that the venous drainage from the hemisphere superiorly, though distorted, was little impeded. There was no papilloedema.

Case 4.—A man, aged 39 years, was involved in a motor-cycle accident, of which details are not available.

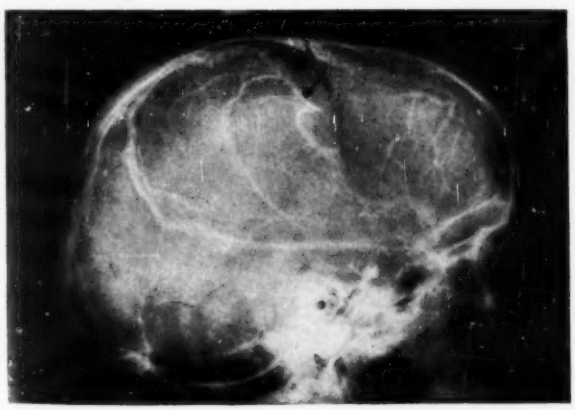

FIG. 5.—Case 4: lateral angiogram.

On admission to hospital soon afterwards the patient was conscious, with amnesia for the accident. Apart from a pulse rate of 48 to 60/min. and extensor plantar responses bilaterally, his condition remained good. On the second day after the accident a left hemiparesis was noted, and transfer to neurosurgical care was arranged. The blood pressure was 130/80 mm. The ocular fundi were still normal. The hemiparesis was of flaccid type, and only the left plantar response remained extensor. A fissure fracture crossed the vault transversely.

The angiogram is shown in Fig. 5, exposed at a normal timing. The preceding films of the series showed a free and active arterial to venous intracranial circulation.

This patient was operated upon because of the onset of a delayed post-traumatic hemiparesis. The large extradural clot, at most 3 cm. thick, was evacuated by right frontal craniotomy.* Next day some motor recovery was noted and was complete by the third day. On discharge from hospital two weeks after operation the plantar responses were almost symmetrical.

Discussion

In all of the cases recorded there was a fracture or diastasis of the vault near the vertex. In addition intracranial hypertension was manifest as a leading clinical feature in three of them. One patient had a lucid interval and the others had a latent period before disturbing neurological signs became evident.

With reference to the first case, the degree of retinal venous engorgement was remarkable. Angiography demonstrated a notable retardation of the circulation in the vessels draining into the sagittal sinus in the Rolandic region overlaid by clot. This was to a lesser extent true also in Case 2. The volume of the clot in Case 1 was small, comparable to that of many clots in the commoner sites, which declare their presence insidiously over many days and cause no alarming syndrome. The hemiplegia was of delayed but rapid onset: its complete disappearance overnight suggests that it may well have been due to cerebral venous obstruction, and particularly compression of thin-walled lacunae. The contrasting angiographic appearance in Case 4 with a voluminous clot is relevant to the argument.

Impairment of the efficiency of resorption of cerebrospinal fluid by the local pressure of extradural clot may perhaps be a lesser factor contributing to intracranial hypertension.

A survey of the literature has so far revealed only three illustrations of comparable angiograms in radiological reports without clinical information (Wickbom, 1949; Pecker, Javalet, and Stabert, 1959; Tiwisina and Stäcker, 1959). It has been learnt, in a personal communication from Professor Pecker, that his case had no papilloedema. He has also

*Operation by Mr. R. M. Varma, now neurosurgical consultant in Bangalore, India.

operated successfully on another patient with a syndrome very similar to that in Case 2.

Lindgren (1960) makes passing reference to a case in which operation was not required.

Petit-Dutaillis, Guiot, Pertuiset, and Le Besnerais (1956) describe a case of haematoma in the posterior fossa revealed by separation of the torcular Herophili from the skull. This patient had not developed papilloedema over a period of observation extending to several days (personal communication from Dr. Le Besnerais). The sinus was of course separated from the skull well posteriorly.

Concerning treatment it is evident that operation is not required in all cases. When the syndrome is florid and acute, or persistent in spite of lumbar puncture, craniotomy seems to be indicated.

These four cases have been encountered in the past four years, so that the condition is probably not rare.

Summary

Four cases of extradural haematoma at the vertex, revealed by angiography, are described; in all, the calvarium was fractured at or near the midline superiorly. In three of the cases papilloedema developed and in two of those operation was necessary.

It is suggested that compression of the lacunae into which the Rolandic veins pour their blood superiorly may be the chief factor in the rise of intracranial pressure noted in the cases, and in the production of the hemiplegia which in one case vanished overnight after removal of a haematoma of relatively small size. In one case the cerebral venous outflow was demonstrably retarded.

I am much indebted to my colleague, Mr. D. G. Phillips of Bristol, for allowing me to include Case 2 in the series. Mr. D. O. Hancock, senior registrar, kindly drew my attention to some of the references, which he had obtained for another paper.

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BOOK REVIEWS

Parkinsonism: Its Medical and Surgical Therapy. By Irving S. Cooper. (Pp. xii + 239; 111 figures. 132*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1961.

There is no doubt that a stereotactic brain lesion properly placed will relieve Parkinsonian tremor and to a lesser degree the rigidity. However, there are plenty of unsolved problems, and in this study by Dr. Cooper there is a frank recognition of the need to select cases very carefully. The best patients to treat are those with unilateral symptoms in which the cause has presumably been an attack of encephalitis many years previously. In the degenerative types of Parkinson's disease which affect one side first, early operation is advised, but the evidence regarding the effect of early operation on the subsequent course of the disease is inadequately studied. Bilateral operations are still unpredictable and hazardous. Attempts to explain the beneficial or the occasional harmful results on physiological grounds have as yet made little progress. This is a dramatic development in neurosurgery but the scientific exploitation of the clinical material is quite inadequate.

Hypothermia for the Neurosurgical Patient. By Antonio Boba. (Pp. vii + 124; 48 figures. 48*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1960.

This short book provides a succinct review of the experimental work and clinical experience in hypothermia techniques suitable for neurosurgical operations. There are three chapters of approximately equal length. The first considers the basic principles of heat exchange and general physiological results; the second discusses the choice of anaesthetic drugs and the complications or disturbances of normal physiology; the third is devoted to details of technique and quotes a few cases. This chapter is the shortest and the book would have been more useful to the practising anaesthetist if it had been the longest. Ether is the recommended anaesthetic drug; as a means of facilitating cooling it has proved useful, but to use it throughout (upwards of five and a half hours in one case quoted) seems a retrogression in anaesthetic practice. Ventricular fibrillation and metabolic acidosis receive much attention as complications to be feared, and one wonders to what extent the universal use of ether may be held responsible for these complications, which are exceedingly rare in the reviewer's experience. Coming from Charles C. Thomas, the book is naturally excellently produced, but 48*s*. seems very expensive.

Essentials of Neurosurgery for Students and Practitioners. By Sean Mullan. (Pp. 288; 87 figures. $6.75.) New York: Springer Publishing Company. 1961.

It must be difficult to write a textbook of neurosurgery which is not too concerned with specialized techniques for students on the one hand, and yet not advanced enough for qualified doctors on the other hand. Professor Sean Mullan, of the University of Chicago, has written such a book, and it is a good one. It is indeed the essentials of neurosurgery as students and practitioners should know them, and the whole field is covered adequately in an easily readable style. There are numerous simple diagrams which for the student are often more helpful than clinical and pathological photographs, and the few ventriculograms and angiograms are well reproduced.

Neurochemistry of Epilepsy: Seizure Mechanisms and their Management. By Donald B. Tower. (Pp. x + 335; 30 figures. 72*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

This book is not intended primarily for biochemists but for any medical practitioner who wishes to understand the essentials of the subject. There are four main subdivisions in the book: oxidative metabolism, amino-acid metabolism, including the role of pyridoxine, electrolytes, and transmitters, and anticonvulsants. The various metabolic disturbances which can produce fits are described, and in the last chapter the author brings all the evidence together in relation to clinical epilepsy. The nature of the basic disorder in epilepsy is still unknown but it may well be that such studies as these are a more profitable line to pursue than the search for anatomically localized foci. Although the book is primarily concerned with epilepsy, anyone who wishes to know the fundamentals of the biochemistry of neurology in general will benefit by reading it.

A Biochemical Basis of Multiple Sclerosis. By Roy L. Swank. (Pp. ix + 88; 14 figures. 40*s*.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Dr. Swank's advocacy of a low-fat diet in multiple sclerosis is well known, but this is only one facet of his wide study of all aetiological factors. These are presented very clearly in this lecture and will be read with profit by those working on this frustrating disease.

The Pathology of Cerebral Palsy. By Abraham Towbin. (Pp. xi + 206; 70 figures. 64*s*.) Springfield, Illinois: Charles C. Thomas; 1960. Oxford: Blackwell Scientific Publications. 1961.

Dr. Towbin, in this book, has ranged far wider than he indicates in the title. Consequently, we are treated to a survey of a large part of paediatric neuropathology,

for example, a description is included of Schilder's disease, mongolism, Krabbe's disease, and Pelizaeus-Merzbacker disease.

This policy has limited the description of the more restricted subject of perinatal cerebral palsy which has been dealt with more thoroughly in contemporary monographs. Nevertheless, Dr. Towbin's account is stimulating reading and he has taken pains to assemble the causes and effects of perinatal brain damage and to present them in a clear, forthright manner. There are numerous excellent illustrations from splendid pathological specimens.

The author's style of writing uses a vocabulary which provokes conflicting reactions. Although it conveys the enthusiasm of the writer for his subject, the reader feels pelted with misused words which add little to their context. Words such as basic, intrinsic, integral, elective, and correlated are used so frequently as to mar their meaning.

The prospective reader may be deterred by the description of this work as on the dust jacket a 'correlated transectional view of the basic pathology of cerebral palsy'. In fact, it is an excellent synopsis of the subject.

Cerebro-Spinal Fluid Dynamics in Health and Disease. By David Bowsher; with Foreword by I. Newton Kugelmass. (Pp. 80; 22 figures. 38*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

The author summarizes the present knowledge of the formation and absorption of cerebrospinal fluid, and an excellent bibliography gives references particularly to methods for the study of C.S.F. dynamics. His chapters on hydrocephalus and other disorders of C.S.F. dynamics are too brief to be of much value, and there is little clinicopathological correlation, but the book indicates the scope for research in this field.

Neuromuscular Disorders (The Motor Unit and Its Disorder). Proceedings of the Association for Research in Nervous and Mental Disease, Dec. 12 and 13, 1958, New York, Volume XXXVIII. Edited by Raymond D. Adams, Lee M. Eaton, and C. Milton Shy. (Pp. xx + 813; 225 figures. 180*s*.) London: Baillière, Tindall and Cox. 1961.

This volume will be welcomed not only by neurologists and those general physicians interested in the disorders of the lower motoneurone, but also by many physiologists, pathologists, and biochemists. The basic problems of structure and function of the motor unit are most ably reviewed and discussed with great clarity by authorities of world renown. Of great interest and importance, too, are the articles on experimental pathology of muscle including the experimental muscular dystrophies. A rather small portion of the book is devoted to the basic approach to clinical problems of neuromuscular disorders in man, and this includes a good description of some physiological techniques useful in the study of neuromuscular disorders. The largest portion of the book, accounting for almost half of it, is devoted to clinical problems. Some of these chapters are extremely well done; the ones on myasthenia gravis and the chronic progressive disorders of the lower motor neurone are outstandingly good and point the way to further advances. The chapter on muscular dystrophy, however, is a rather disappointing attempt at clinical classification and encyclopaedic description which seems to be a long-winded way of saying how little is understood about them at the moment.

The volume ends with an all-too-short section on some experimental techniques of promise in the study of neuromuscular disorders. This section is quite fascinating and will be read with pleasure and eagerness by everyone who has contact with patients suffering from disorders of motor units.

The late Dr. Lee Eaton was largely responsible for the programme of subjects and for inviting the various speakers—all experts in their field. This volume will long remain as an outstanding memorial to him and one of the most important contributions of the A.R.N.M.D. since the 1940s. It is a pity that it has taken so long to publish the volume after the presentation of the papers (December 1958 to June 1961).

Lehrbuch der Psychiatrie, 10th ed. By Eugen Bleuler; revised by Manfred Bleuler, with Foreword by Manfred Bleuler. (Pp. xvi + 629; 121 figures. DM 56.) Berlin: Springer-Verlag. 1960.

This book appeared first in 1916, and represented an attempt by Eugen Bleuler to apply to the whole of psychiatry the principles of his approach to schizophrenia, which he had published in 1911 in the classic 'Dementia Praecox or the Group of Schizophrenias'. Eugen Bleuler died in 1939, and the subsequent four editions of the book have been revised and edited by his son Manfred. In those early days Bleuler tried to introduce the ideas of psychoanalysis into psychiatry and to integrate them with Kraepelian nosology. In his attitude towards the psychoanalysis of his time he was more open-minded than most European psychiatrists of his day; but even so he admitted only a very modified (psychoanalysts might say watered down) version of Freud's views. What he achieved was rather an eclectic assimilation of some early psychoanalytical ideas than a true integration of principles. In a letter of 1908 to Abraham, quoted by Jones (1958), Freud wrote, 'Jung himself writes to me that Bleuler is showing himself amenable and almost inclined to abandon the conception of the organic nature of dementia praecox'. But in actual fact, he never did. He left the question of the causation of the psychoses essentially open, favouring a multiple causality and coming fairly close to the position later developed by Kretschmer.

Every new edition of the book has been carefully kept up to date by Manfred Bleuler. In the present edition the chapter on drug treatment is new, and those on epilepsy and on psychotherapy and causation in the neuroses have been partly re-written. The textbook has its established postion in the German-speaking psychiatric world, which it earns by its clear organization of the material and excellent sense of balance.

The first edition of the book was translated into

English by Brill in 1923. Apart from the fact that the translation is not a very happy one, the book has by now changed so greatly that the English translation is of no more than historical interest.

Experimental Psychology. By Burton G. Andreas. (Pp. xi + 595; 19 figures. 56*s.*; $6.95.) New York and London: John Wiley. 1960.

This textbook is unusual in two respects. First, it takes seriously the problem of teaching experimental psychology as opposed to the mere imparting of selected information; and secondly, it makes no attempt to cover the whole field of contemporary inquiry. The first part is concerned mainly with general methods; a good deal of attention is given to the design and conduct of experiments, the nature of psychological measurement, and the relation of observation to theory. (Even the writing of research reports finds mention, though here it is a pity that greater stress is not laid on good and simple English.) The second part deals with some selected areas of investigation, including sensory processes, perception, association, and learning. On the whole, this book is informed and thoughtful though it fails to transcend the conventional limits of American psychology and can hardly be said to imbue the student with a sense of adventure. Although addressed to university teachers of psychology and their students, it might prove useful to neurologists and others seeking guidance on methodological issues.

Sensory Deprivation. Edited by P. Solomon *et al.* (Pp. xv + 262; 21 figures. 46*s.*) Harvard University Press (London: Oxford University Press). 1961.

Recent experimental work on human volunteers and animals has shown that normal brain and thought processes become disorganized (often with hallucinations) if the normal afferent bombardment of the central nervous system from skin, eyes, and ears is prevented. Such deprivation in animals from birth has even more startling effects for it prevents the development of a great variety of normal reactions. This is an important new field of research and its presentation in this volume will arouse great interest.

Brain Mechanisms and Learning. A Symposium organized by the Council for International Organizations of Medical Sciences. (Pp. xiv + 702; illustrated. 70*s.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas; Toronto: Ryerson Press. 1961.

This symposium was held in 1959 and is concerned with biological problems which are of increasing interest at the present time. A scholarly introduction by H. W. Magoun provides a vivid setting for the papers which follow. These include contributions from R. W. Gerard, D. O. Hebb, W. H. Thorpe, J. Konorski, J. C. Eccles, W. R. Adey, C. Estable, and many others.

The main problems discussed are concerned with the physical changes which must take place in nerve cells when they are involved in establishing a simple memory mechanism, and in order to investigate this there are studies of surprising diversity. Thus the tail half of a flatworm that is cut in two not only grows a new head but retains a pattern of directional behaviour which had been taught to the intact worm. A chaffinch requires to hear the correct song of the species during its first Spring in order to perform correctly, and many other aspects of animal behaviour generally thought to be inborn are in fact acquired after birth. Nerve cells may communicate with each other in several different ways but the precise mechanism of the potentiation at synaptic connexions which has been demonstrated in monosynaptic responses remains very uncertain. Yet synaptic potentiation in response to repetitive activity provides the most probable physiological background to memory and learning processes.

Fear and Depression: Their Causes and Self-Treatment. By Allan Worsley. (Pp. 84, plus Foreword and Index. 8*s.* 6*d.*) London: George Allen and Unwin. 1961.

This little book first appeared in 1939 and is now in its eighth edition. Its author has since 'turned over wholly to gynae-psychology, that is, the whole-time study and specialized speciality of the feminine mind and its troubles'. His aim is to provide methods based on modern knowledge of psychology for dealing with the exacerbation of fear and depression consequent upon the upheavals of World War II, and is in line with the many popular treatises for those distressed in mind which have appeared since English books started to be printed in the vernacular in the sixteenth century.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Drugs in the Treatment of Disease. Specially commissioned articles from the *British Medical Journal*, 1961 (35*s.*).

Enjuiciamiento de la Medicina Psicosomatica. By Honorio Delgado. (Pp. 179. Price not stated.) Barcelona: Editorial Científico Médica. 1960.

Patologia Mentale e Farmacologia. By Antonio Bastrieri. (Pp. xi + 258. Lira 3500.-.) Padova: Cedam. 1961.

Il Lobo Parietale. By Carlo Gentili; Foreword by P. Ottonello. (Pp. 406; illustrated. Price not stated.) Bologna: Officina d'Arte Grafica Cacciari. 1955.

The Neoplastic Process and the Nervous System. P.S.T. Cat. No. 203 (63*s.*): **The Control of Immunogenesis by the Nervous System.** P.S.T. Cat. No. 124 (60*s.*): **Works of the Institute of Higher Nervous Activity Physiological Series,** Vols. 1 and 2. Cat. No. 69 (74*s.*) and No. 71 (64*s.*); **Pathophysiological Series,** Vols. 1, 2, and 3. Cat. Nos. 70, 72, and 74 (78*s.* each). Program for Scientific Translations, P. O. B. 7145, 14 Shammai Street, Jerusalem.

Motor Examination of Peripheral Nerve Injuries. By Y. T. Oester and John H. Mayer, Jr. (Pp. vi + 89; 101 figures. 44*s.*) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

Analysing Qualitative Data. By A. E. Maxwell. (Pp. 163. 16*s*.) London: Methuen. 1961.

Handicapped Children. By John D. Kershaw. (Pp. x + 228. 21*s*.) London: Wm. Heinemann Medical Books. 1961.

Psychosomatic Aspects of Pediatrics. Edited by Ronald MacKeith and Joseph Sandler. (Pp. xiv + 155. 50*s*.) London, New York, Paris: Pergamon Press. 1961.

The Chemistry of Brain Metabolism in Health and Disease. By J. H. and David M. J. Quastel. (Pp. xi + 170. 52*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1961.

Neural Mechanisms of the Auditory and Vestibular Systems. Edited by Grant L. Rasmussen and William F. Windle; Foreword by Richard L. Masland. (Pp. xiv + 422; 225 figures. 126*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

Multiple Sclerosis Prognosis and Treatment. By Leo Alexander, Austin W. Berkeley, and Alene M. Alexander. (Pp. xvi + 188; 63 figures. 60*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1961.

Kernicterus and Its Importance in Cerebral Palsy. A Conference presented by The American Academy for Cerebral Palsy, Eleventh Annual Meeting, New Orleans, Louisiana. (Pp. xi + 306; illustrated. 70*s*.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1961.

Guildhall Lectures 1960. Papers by Professor George W. Beadle, Professor H. J. Eysenck, and Lord Adrian. (Pp. 105; 13 figures. 4*s*. 6*d*.) University of London Press. 1961.

THE AUGUST (1961) ISSUE

The August (1961) issue contains the following papers:—

Epilepsy Due to Small Focal Temporal Lesions with Bilateral Independent Spike-discharging Foci: A Study of Seven Cases Relieved by Operation. Murray A. Falconer and Walter A. Kennedy
Mental Deterioration in Epileptic Children. M. R. Chaudhry and D. A. Pond
The Diagnostic Use of the McGill Picture Anomaly Test in Temporal Lobe Epilepsy. Denis C. Shalman
Histological and Chemical Findings in Krabbe's Leucodystrophy. R. M. Norman, D. R. Oppenheimer, and A. H. Tingey
Infantile Metachromatic Leucodystrophy. J. W. Black and J. N. Cumings
The Effects of Hemispherectomy on Intellectual Functioning in Cases of Infantile Hemiplegia. John McFie
Four Cases of Carotid-basilar Anastomosis Associated with Central Nervous System Dysfunction. Robert L. Campbell and Mark L. Dyken
Defects in Indentifying Objects Visually in a Patient with Cerebrovascular Disease. E. Ettlinger and Maria Wyke
Flicker Fusion in Multiple Sclerosis. A. F. Titcombe and R. G. Willison
The Effect of Anxiety on Time Judgment and Time Experience in Normal Persons. Samuel I. Cohen and Alexander G. Mezey
The Effect of Depressive Illness on Time Judgment and Time Experience. Alexander G. Mezey and Samuel I. Cohen
The Absorption of Tri-ortho-cresyl Phosphate Through the Skin of Hens and Its Neurotoxic Effects. P. Glees and W. G. White
A Case of 'Pure' Word Blindness. A. Kreindler and V. Ionăşescu
Ophthalmodynamometry in Carotid Artery Disease. R. W. Ross Russell and W. I. Cranston
Apparatus for Measuring and Counting Myelinated Nerve Fibres. M. L. E. Espir and D. T. C. Harding
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A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s*. 6*d*.

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Word blindness, 'pure', 275
WRAY, S., *see* CLARKE, P. R. R., and WRAY, S.
WYKE, M., *see* ETTLINGER, G., and WYKE, M.

VOL. 24 (New Series) No. 4 NOVEMBER, 1961

JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY

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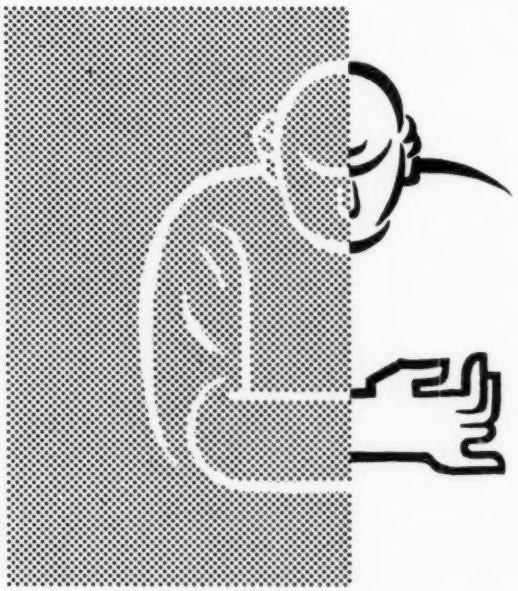

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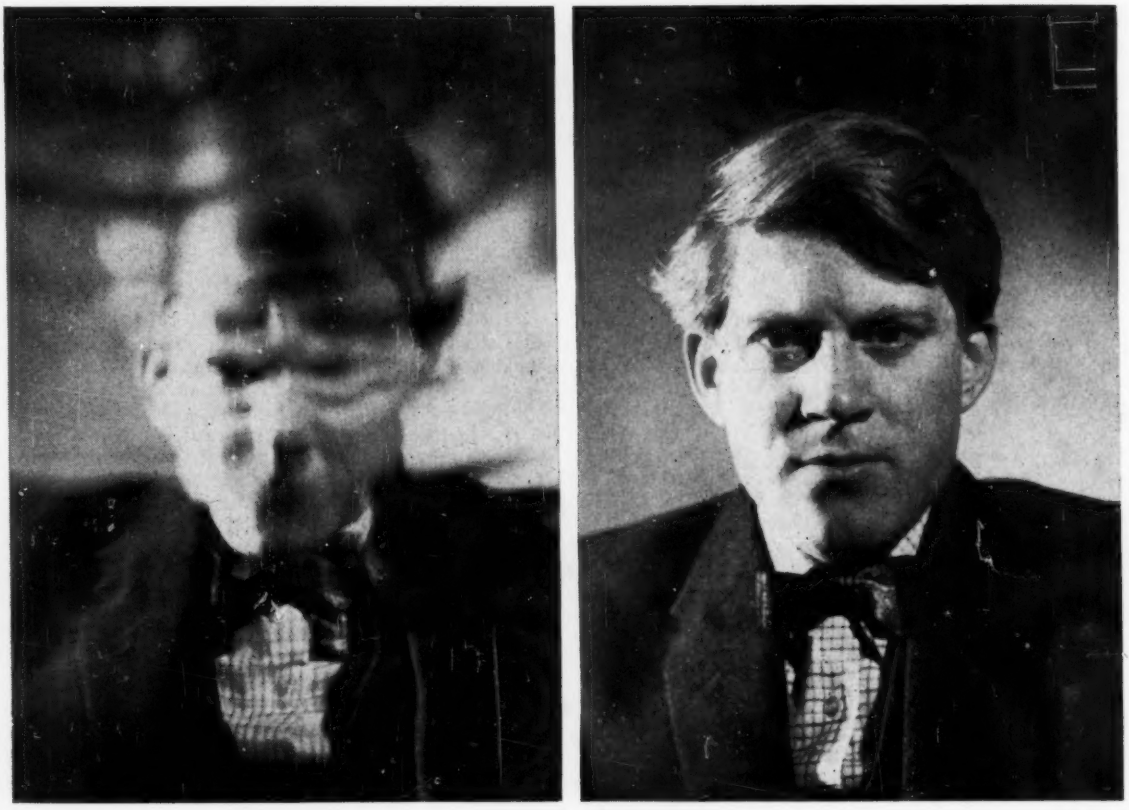

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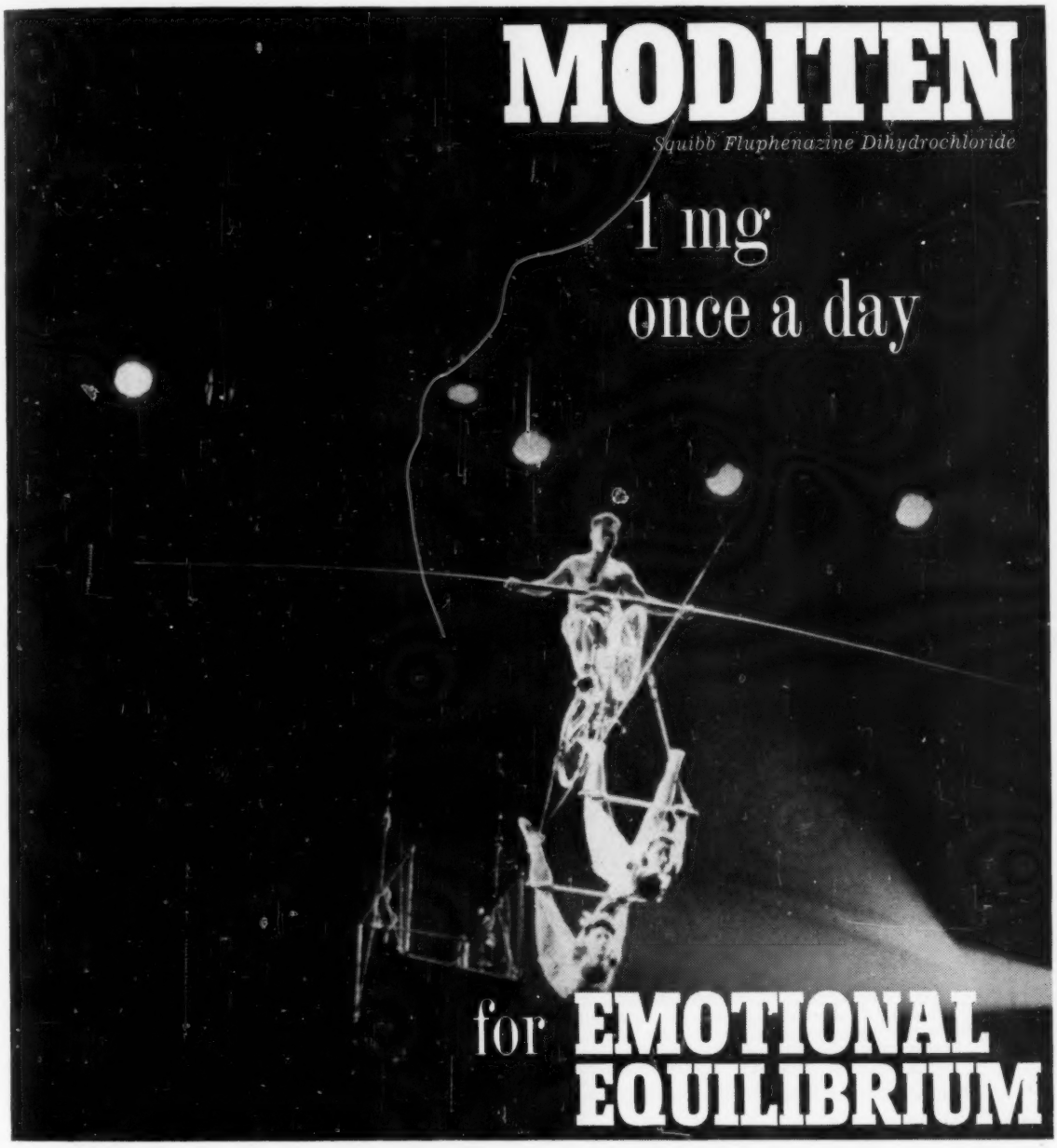

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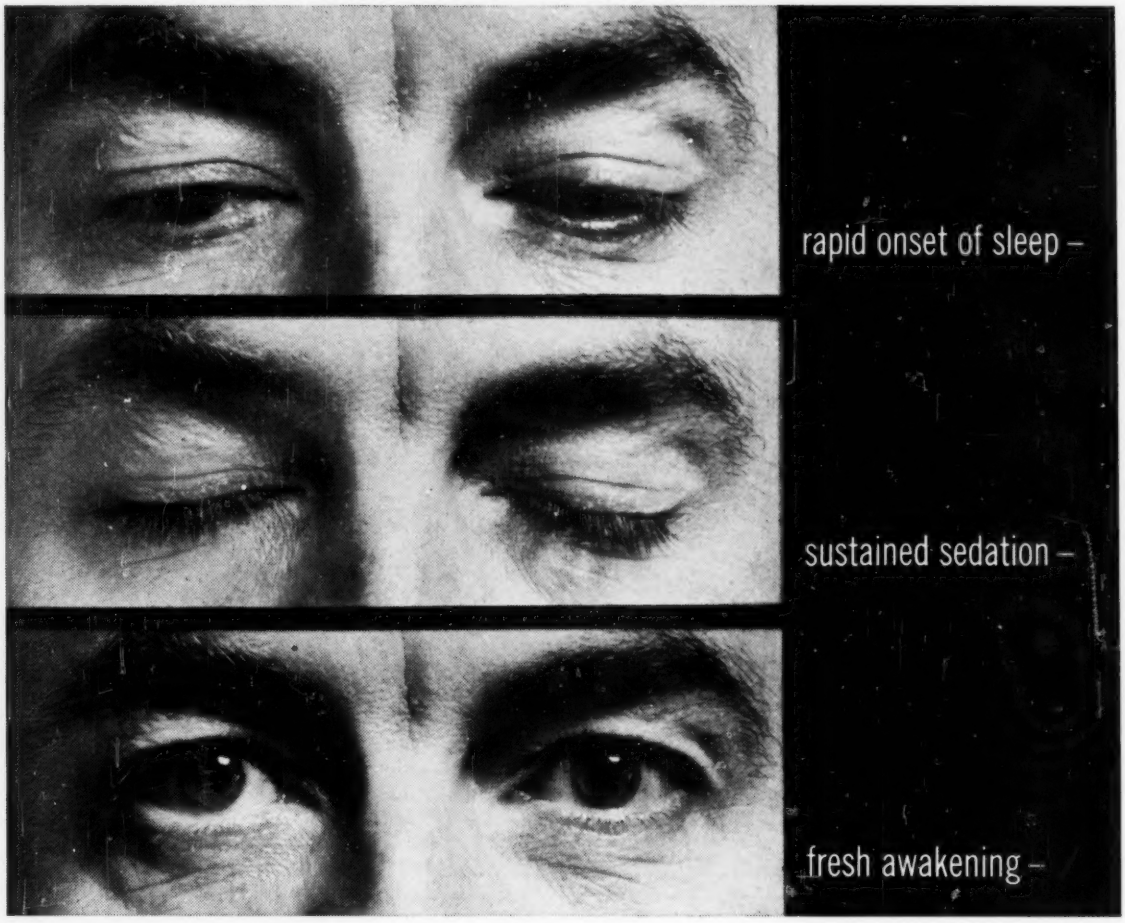

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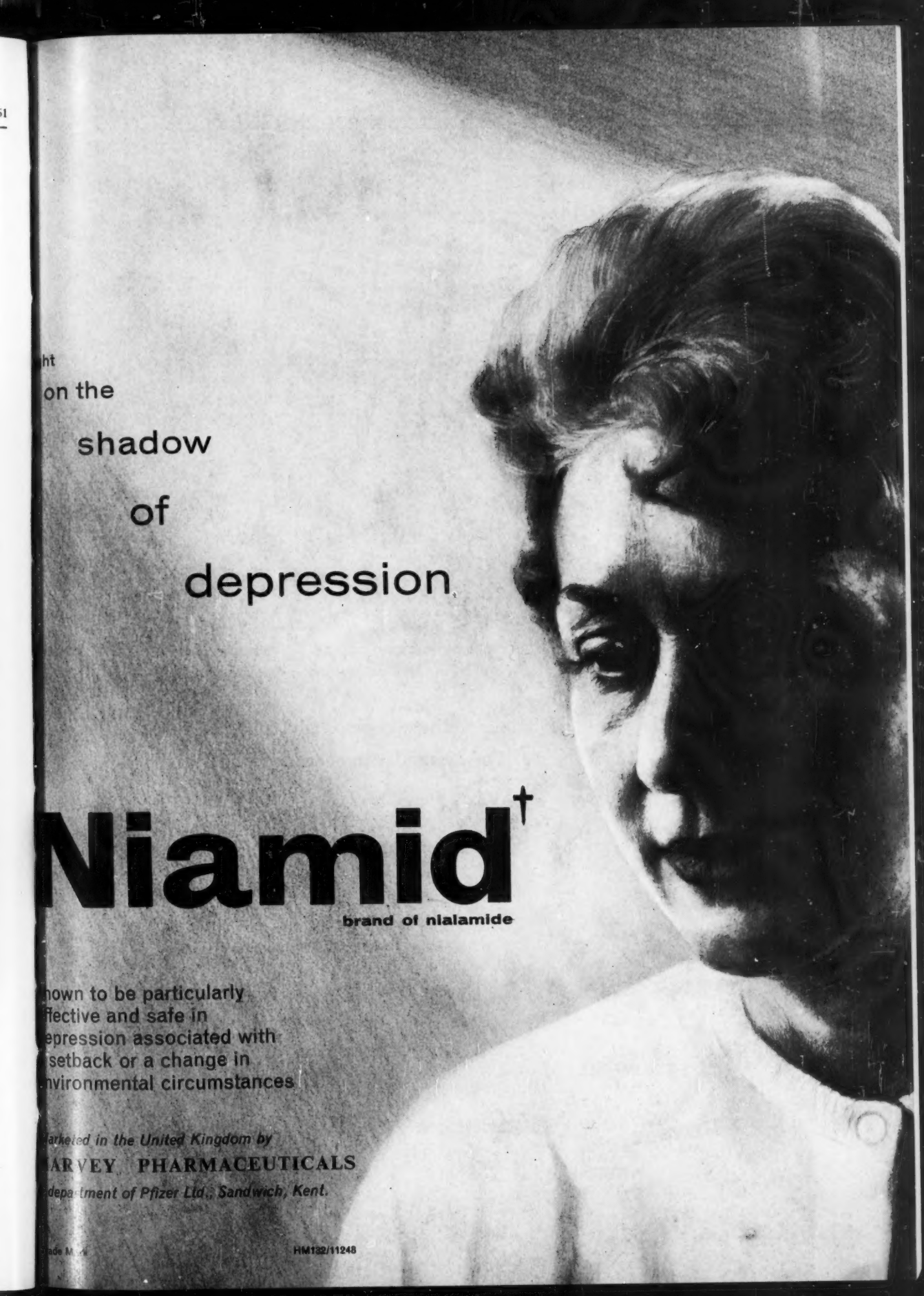
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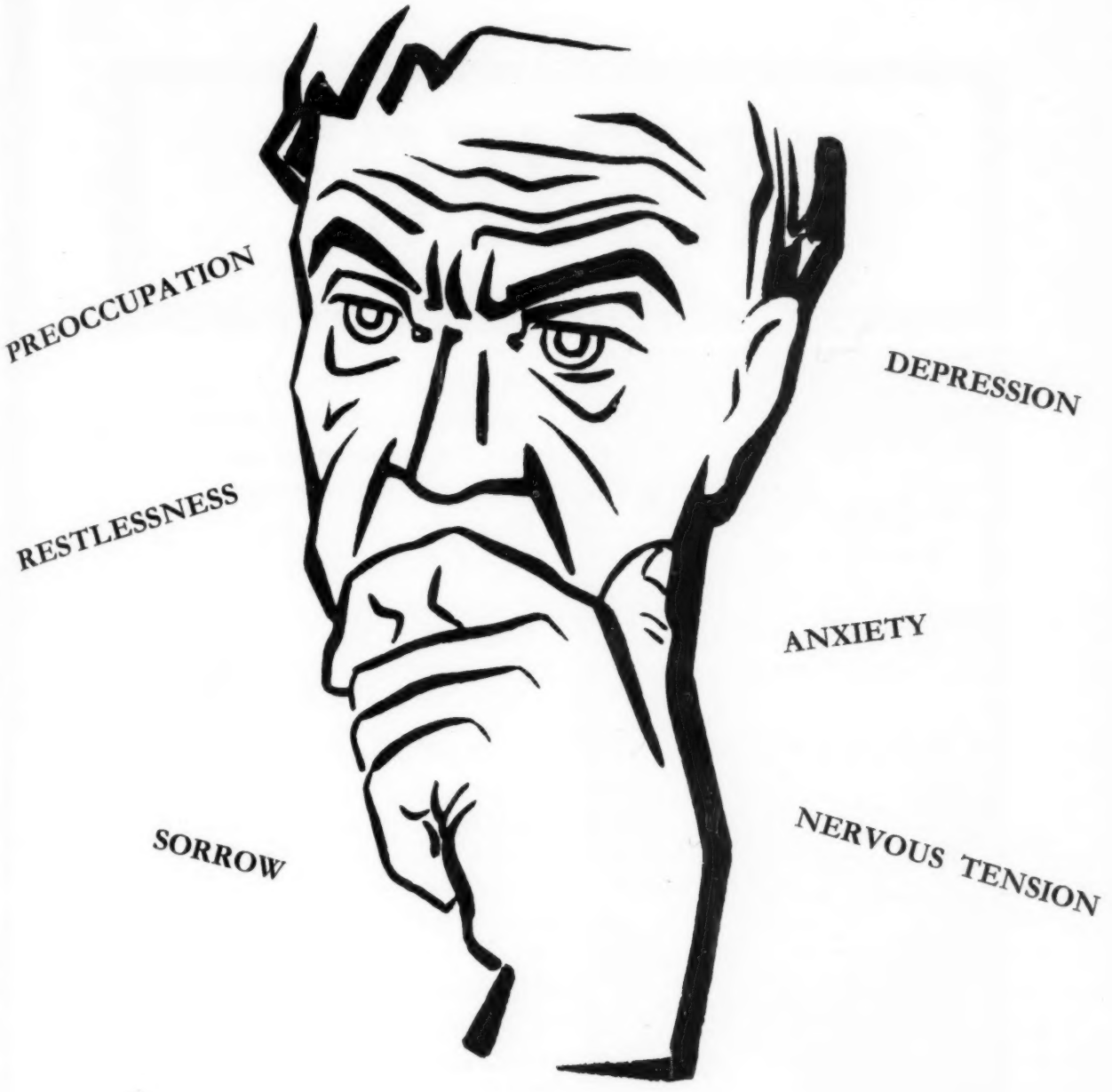

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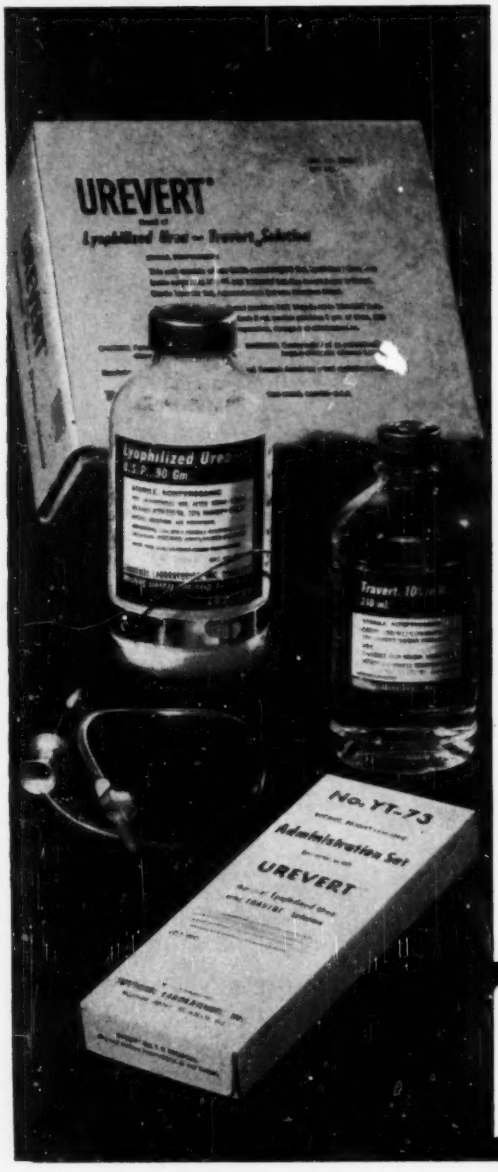

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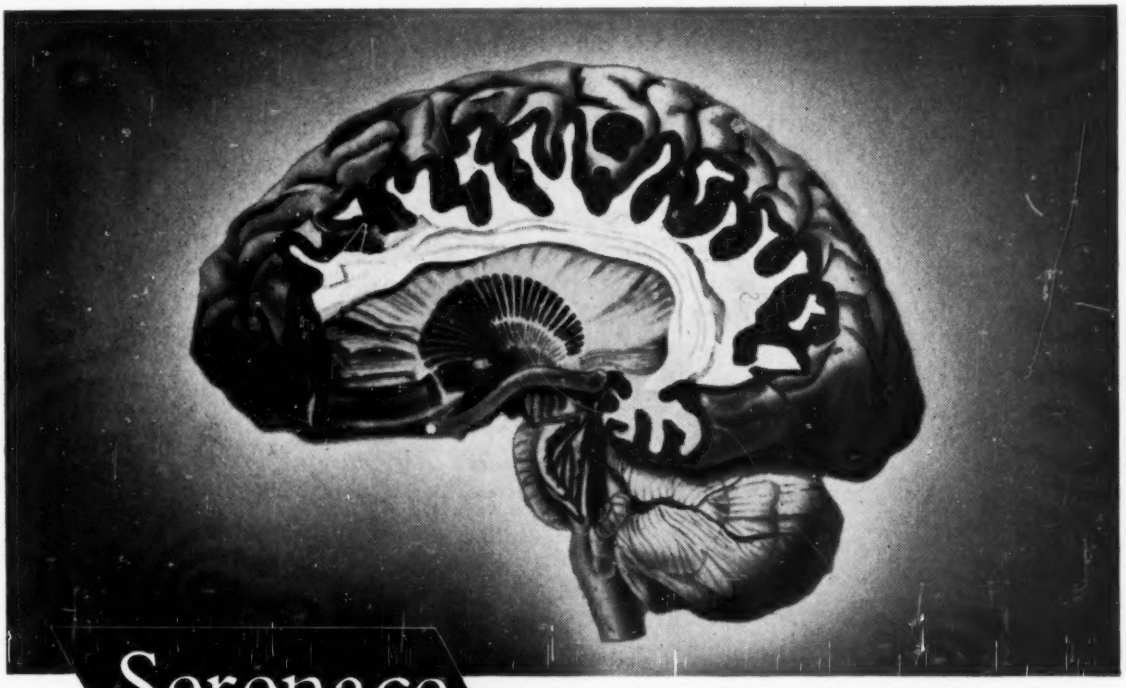

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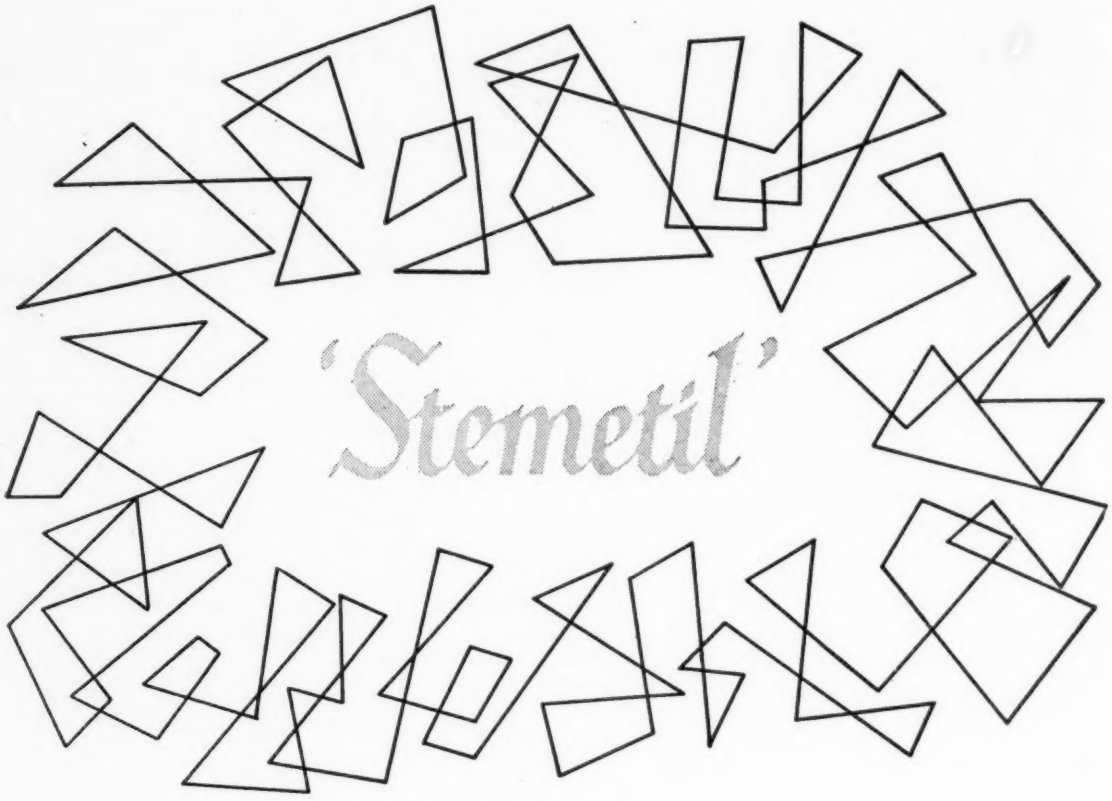

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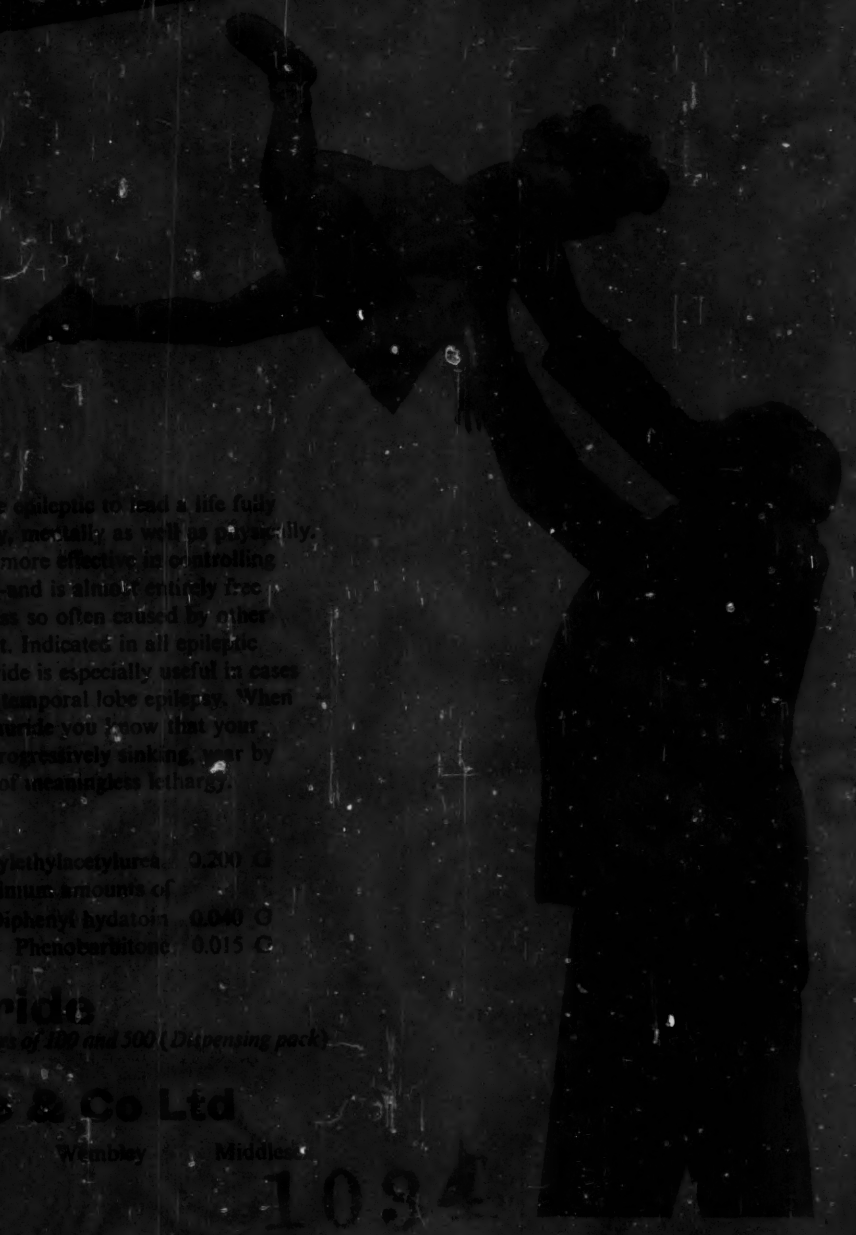

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